This document was submitted to EPA by a registrant in connection with EPA's evaluation of this chemical, and it is presented here exactly as submitted.

TITLE

Comments From Cheminova A/S on EPA's
Draft Preliminary Risk Assessments for Malathion

DATA REQUIREMENT

Not Applicable

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COMPLETION DATE

March 29, 2000

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Not Applicable

STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS

No claim of confidentiality is made for any information contained in this document on the basis of its falling within the scope of FIFRA §10(d)(1)(A), (B), or (C).

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CERTIFICATION OF GOOD LABORATORY PRACTICE

This document is a response to EPA's preliminary draft Health Effects Division and Environmental Fate and Effects Division Chapters of the Reregistration Eligibility Decision Document for malathion. As such, Good Laboratory Practice Standards (40 CFR Part 160) are not applicable to this submission.

Submitter: _____ Date: _____

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I. INTRODUCTION

Cheminova A/S (Cheminova) is respectfully submitting these comments on the draft preliminary risk assessments for malathion prepared by EPA's Health Effects Division (HED) and the Environmental Fate and Effects Division (EFED).

Cheminova has a long track record of compliance with all federal testing, labeling, packaging, and formulation requirements for malathion and its other pesticide products. Over the past several years, Cheminova has conducted and submitted many studies to fully define the toxicity and environmental behavior of malathion. These studies have all been submitted to the Office of Pesticide Programs in accordance with EPA's schedule for data submission to support the reregistration of Cheminova's technical malathion.

These comments provide EPA with additional information about malathion and its supported use patterns. This additional information should enable the Agency to conduct a more accurate assessment of any potential risks to human health, non-target species, and the environment than is presented in the draft HED and EFED preliminary risk assessments.

Finally, Cheminova adopts and incorporates by reference in these comments the document entitled, "A Science-Based, Workable Framework for Implementing the Food Quality Protection Act" (Implementation Working Group (IWG), June 1998), which the IWG has submitted to EPA.

II. CHEMINOVA'S COMMENTS ON ERRORS

Cheminova has identified the following errors in EPA's draft preliminary risk assessments.

A. ERRORS IN THE DOCUMENT ENTITLED "CANCER ASSESSMENT DOCUMENT: EVALUATION OF THE CARCINOGENIC POTENTIAL OF MALATHION" DATED FEBRUARY 2, 2000

- In the Executive Summary, page iv, 2nd paragraph: EPA references "Attachment 1." Because the attachments are not numbered (and the first of the documents does not mention malaoxon), it is unclear which document EPA is referring to. Cheminova requests that when EPA revises this document, the references to attachments are clearer.

- In the Executive Summary, page v, first paragraph: The last sentence of this paragraph states that "…and tumors of the nasal mucosa at 6000 ppm, ….nasal tumors were also seen at 12,000 ppm…" The use of the word tumors is incorrect because only one tumor was seen in female rats at each dose level. Cheminova requests that when EPA revises this document, this statement is corrected so that it accurately reflects the results of the study.

- There is no "page 4" in the document provided to Cheminova. It appears that this is a pagination error rather than a page missing from the document.

- Page 28, first paragraph, line 7: EPA states that "For cholinesterase inhibition, the overall NOAEL was 50 ppm and the LOAEL was 5000 ppm…" in the subchronic inhalation toxicity study in the rat. However, based on statistically significant inhibition, 5000 ppm was a clear NOAEL and 20,000 ppm was the LOAEL for brain cholinesterase inhibition in this study.

- Page 28, second paragraph, line 7 from the bottom: EPA states that the subchronic inhalation study did not established a NOAEL for plasma and RBC cholinesterase inhibition. However, based on statistically significant inhibition, a clear NOAEL of 0.1 mg/L was established for blood and brain cholinesterase inhibition in this study.

- Page 29, first paragraph, last sentence: EPA states that "Based on the re-assessment of the nasal tissues, for males, the NOAEL was 100/50 ppm and the LOAEL was 500 ppm based on non-neoplastic lesions of the nasal mucosa; a NOAEL was not identified for females" in the malathion chronic toxicity/oncogenicity study in the rat. However, the peer review of the nasal tissues conducted by Dr. Swenberg (MRID #44782301) concluded that the NOAEL for toxicity in the rat nose, for both sexes, was 500 ppm. Therefore, EPA's statement is wrong and needs to be corrected.

B. ERRORS IN THE DOCUMENT ENTITLED "MALATHION TOXICOLOGY CHAPTER OF THE REREGISTRATION ELIGIBILITY DOCUMENT (RED)" DATED MARCH 24, 1998

- Table 1 identifies the requirements for subchronic and chronic dog toxicity studies as being satisfied. However, the HIARC reports are requiring additional testing. EPA needs to clarify this requirement.

- Table 1 identifies the requirement for subchronic inhalation toxicity in the rat to be satisfied. However, the HIARC documents are requiring a new study. EPA should clarify this requirement.

- On page 8, second paragraph, line 2: the malathion purity should be 96.4%, not 97.1%.

C. ERRORS IN THE DOCUMENT ENTITLED "MALATHION : REVISED NOAEL FOR DERIVATION OF THE CHRONIC REFERENCE DOSE- REPORT OF THE HAZARD IDENTIFICATION ASSESSMENT REVIEW COMMITTEE" DATED NOVEMBER 1, 1999

- Page 2, paragraph 2, line 2: the malathion purity should be 96.4%, not 97.1%. In addition, the mid dose level should be 6000 ppm, not 600 ppm.

- Page 2, Paragraph 4, lines 2 and 3: the dose levels listed in parentheses should be 100 ppm for 1 to 16 weeks and 50 ppm for 18 to 102 weeks.

D. ERRORS IN THE DOCUMENT ENTITLED "MALATHION REEVALUATION: REPORT OF THE HAZARD IDENTIFICATION ASSESSMENT REVIEW COMMITTEE" DATED DECEMBER 22, 1998

- On page 4, the fourth line from the bottom of the page: the sentence should read "…the acute neurotoxicity study in rats (NOEL = 1000 mg/kg, LOEL = 2000 mg/kg)…" not "1000 mg/kg/day" and "2000 mg/k."

- On page 5, in Question 3: the first sentence should read "…a single intraperitonial dose as low as 50 mg/kg in the rat…", not "50 mg/kg/day".

- On page 9, 6th paragraph, line 5: The purity of malathion should 96.4%, not 97.1%.

- Page 20, DER #8: The guideline referenced for an acute delayed neurotoxicity study should be 81-7, not 83-3.

- Page 21, DER #14: The guideline referenced should be 84-2, not 82-2.

- Page 21, DER #15: The guideline referenced should be 84-2b, not 82-2b.

- Page 21, Document #2, line 3: The guideline referenced should be 83-2, not 830-2. In addition, the word "ice" at the end of the third line should be "mice".

- Page 21, Document #2, line 4: The word "malaxon" should be "malaoxon".

E. ERRORS IN THE DOCUMENT ENTITLED "MALATHION REEVALUATION: REPORT OF THE HAZARD IDENTIFICATION ASSESSMENT REVIEW COMMITTEE" DATED DECEMBER 17, 1997

- The top of the first page of this document should read "ATTACHMENT 2: HIARC Report of 12/17/97" not "HIAR"

- Page 51, Section B: the malathion purity should be 96.4%, not 97.1% and the mid dose level was 6000 ppm, not 600 ppm.

- Page 52, third paragraph, fifth line: the purity should be 96.4%, not 97.1%.

- Page 54, under Dose and Endpoint for Risk Assessment: the word "plasma" should be deleted from the first sentence because there was no statistically or biologically significant inhibition of plasma cholinesterase for males or females in the 300 ppm dose group in the 21-day rabbit dermal toxicity study.

F. ERRORS IN THE DOCUMENT ENTITLED "MALATHION: OCCUPATIONAL AND RESIDENTIAL EXPOSURE AND RISK ASSESSMENT FOR THE RED DOCUMENT" DATED SEPTEMBER 16, 1999

- In Table 6, under scenario 1c (mixing/loading liquids for airblast sprayer) of the 9/99 risk assessment, the dermal unit exposure is listed as 0.23 mg/lb a.i. for the "gloves" scenario (applicable to "ag citrus" and "ornamentals" only). However, the correct dermal unit exposure is 0.023 mg/lb a.i. for this scenario. Thus, there is a 10-fold error in the dermal exposure calculations for this scenario. Cheminova requests that EPA correct this error and apply the PPE assumptions consistently in this and every scenario.

- On page 39 of the occupational risk assessment, the abbreviation "$LADD_{int}$" is used to refer to the internal lifetime average daily dose in the second formula. However, the previous formula and the explanation for the second formula use the abbreviation "$LADD_{abs}$." Cheminova requests that EPA address this inconsistency of notation.

- EPA is not consistent in how many significant figures it presents its exposure calculations. It is not appropriate to present exposure estimates to a degree of precision that is not associated with the inputs that went into generating the estimates. For example, unit exposures are specified to two significant figures, so the associated exposure estimates should not contain more than two significant figures. Cheminova recommends that EPA revise the calculations to present only two significant figures.

- In the text, numbers are frequently presented in a form of scientific notation that is incorrect. In spreadsheets, the custom is to present the number 0.000001 as 1E-06. This format is recognizable and understood in numerical tables by the reader. However, in the 2/00 text, EPA presents the number 0.000001 as $1.0e^{-06}$. This presentation is incorrect. The lower case "e" refers to the exponential function in mathematics. In the text, EPA should use the format 1E-6. Cheminova recommends that the revised risk assessment include only properly recognized versions of scientific notation.

G. ERRORS IN THE DOCUMENT ENTITLED "EFED RED CHAPTER FOR MALATHION"

- Cheminova believes that EFED has inappropriately extrapolated information obtained from the use of malathion in the boll weevil and Medfly eradication programs, and adult mosquito control (a human health use) for conducting its environmental risk assessments. Cheminova does not consider these programs to be representative of typical agricultural

practice; these uses are special programs directed by government agencies that include use patterns (general area applications using ULV formulations) that are not representative of general agricultural practices. Cheminova believes that it is inappropriate for EPA to draw general conclusions from these special uses about the potential for malathion to contaminate ground water, surface waters, and drinking water from typical agricultural uses. Rather, EPA should conduct risk assessments for each of these special programs separate from typical agricultural uses.

- EFED has conducted its ecological risk assessment using a use rate for cotton that includes up to 25 applications per year. Cheminova notes that the 25 applications per year are included on labels to accommodate the boll weevil eradication program. Typical agricultural use of malathion includes no more than 8 applications per year (3 early season and up to 5 late season applications). USDA notes that after the boll weevil is eradicated, the use of all insecticides (including malathion) on cotton will be reduced to three or fewer applications per year. Cheminova believes that EFED should conduct an ecological risk assessment based on how malathion is typically used in general agriculture rather than for a use pattern meant for the boll weevil eradication program and believes that EFED should work with USDA concerning potential risks associated with the Boll Weevil eradication program.

- On page 6 of the EFED chapter, EFED states that all technical malathion produced in the U.S. is manufactured by Cheminova. This statement is inaccurate. Cheminova does not produce any technical malathion in the U.S., it is produced in Denmark and shipped to the U.S.

- Page 8 of the EFED chapter is a blank page.

- Cheminova confirms that it holds one Federal registration of a mixture formulation of malathion and methoxychlor (EPA Registration No. 67760-2). However, this formulation is not currently marketed or sold in the United States.

- Cheminova believes that risk assessments should only be performed for the use patterns being supported for reregistration. Once the final RED is issued, EPA should take appropriate steps to assure that product labeling is amended to reflect only those use patterns approved for reregistration.

- The following crops are not listed in EFED's Table 1: Brussel sprouts, cantaloupe, cauliflower, collards, kale, kohlrabi, peppermint, and trefoil. Cheminova assumes that cantaloupe is covered by melons. According to the residue chemistry section of EPA's document, the maximum supportable use rates for these crops, based on available residue data, are 1.25, 1.0, 1.25, 1.25, 1.25, 1.25, 0.94, and 1.25 lbs ai/A, respectively.

- In Table 1, EFED has written "pepper and spearmint". Cheminova assumes that EFED means "peppermint and spearmint". This is easily mistaken to mean peppers rather than peppermint. EPA should clarify this point.

- In Table 1, EFED lists a maximum application rate of 1.25 lbs ai/A for chayote root and chayote fruit. However, according to the residue chemistry section of EPA's document, the maximum supportable use rate, based on available residue data, is 1.5 lbs ai/A.

- In Table 1, EFED lists a maximum application rate of 0.94 lbs ai/A for mushrooms. However, according to the residue chemistry section of EPA's document, the maximum supportable use rate, based on available residue data, is 1.7 lbs ai/A.

- In Table 1, EFED lists a maximum application rate of 1.0 lbs ai/A for squash. However, according to the residue chemistry section of EPA's document, the maximum supportable use rate, based on available residue data, is 1.0 lbs ai/A for winter squash and 1.88 lbs ai/A for summer squash.

- In Table 1, EFED lists a maximum application rate of 1.25 lbs ai/A for sweet potatoes. However, according to the residue chemistry section of EPA's document, the maximum supportable use rate, based on available residue data, is 1.56 lbs ai/A.

- EFED included the use of malathion on ornamental lawns, turf, and golf courses. As noted in its March 10, 1998, letter to EPA, Cheminova is not supporting this use for reregistration. Thus, EPA should delete this use from its risk assessments.

- In its description of the environmental fate of malathion, EFED compares the results of registrant submitted guideline studies to results from studies obtained from the open literature. EFED presents the information from the open literature in such a way that it appears to give equal weight to the results from the open literature studies. Cheminova believes that the registrant-submitted, guideline studies, conducted in compliance with Good Laboratory Practices and conducted with Cheminova's test material, should be given much more weight than studies from the open literature. If EFED wants to include information from the open literature, it should fully evaluate these studies, provide data evaluation records for these studies, identify discrepancies and ambiguities and seek to eliminate them by follow up with the study authors, determine the availability of underlying raw data, and include a discussion of the problems and uncertainties associated with these studies like it does with the registrant submitted studies.

- In its discussion about spray drift on page 26, EFED indicated that in 1998 it planned to complete its evaluation of the studies conducted and submitted by the Spray Drift Task Force. If EFED has completed this review, it should update this section of the document.

- In the Pesticide Root Zone Model (PRZM) files provided by EFED to Cheminova, two errors were found for the citrus scenario. First, there was an application date of June 31st for each year in the scenario. The date was changed to June 30th, but the final result for the scenario was unchanged. Additionally, the value for the K_{oc} was not entered correctly. The correct value is 151 ml/g, but PRZM was reading the value as 15 ml/g in the EPA scenario. These errors should be corrected.

- EFED states that malathion has been implicated in numerous fish kill incidents over its five decades of use. EFED needs to provide references for this statement. Furthermore, if the references cited by EFED do not demonstrate that malathion is the cause of these incidences, then EFED should not cite these references.

III. CARCINOGENICITY CLASSIFICATION FOR MALATHION

Cheminova A/S (Cheminova) disagrees with the conclusion of EPA's Cancer Assessment Review Committee (CARC) that malathion should be classified as a "likely human carcinogen" (USEPA, 2000). That classification was based primarily on one rat study in which the study pathologist originally diagnosed treatment-related liver tumors in female rats at doses that CARC did not consider to be excessive. A recently completed rediagnosis by a Pathology Working Group (PWG) resulted in significant changes in these diagnoses; the study pathologist was a member of the PWG and agreed with the new diagnoses. Based on these rediagnoses and significant deficiencies in other aspects of the CARC review, Cheminova concludes as follows:

- CARC's classification of malathion as a "likely human carcinogen" is scientifically unsupportable;

- Even in the absence of the new PWG information, CARC's weight-of-the-evidence evaluation is not appropriate; and

- The total weight of scientific evidence clearly dictates classification of malathion as "unlikely to be carcinogenic to humans."

A. NEW PATHOLOGY WORKING GROUP REVIEW

1. Results

After reviewing the CARC Cancer Assessment Document and seeing the importance CARC was placing on the female rat liver tumors in the 1996 malathion chronic toxicity/ oncogenicity study (Daly, 1996a, MRID 43942901), Cheminova decided to seek a more complete review of the slides in question. As required by PR Notice 94-5 (August 24, 1994), the new review consisted of two steps. Both of these steps were conducted in full compliance with the procedures described in PR Notice 94-5.

First, Cheminova requested a pathology peer review of all liver slides from female F-344 rats from the study by a peer review pathologist (PRP), Dr. William Busey of Experimental Pathology Laboratories, Inc. The peer review was conducted on March 14, 2000, at Huntingdon Life Sciences (HLS), the laboratory that performed the study, in East Millstone, New Jersey. Dr. Henry Bolte, the original study pathologist (SP), was present during Dr. Busey's review.

Second, a Pathology Working Group (PWG) consisting of Drs. Jerry Hardisty (Chair), Paul Hildebrandt, Robert Garman, and Michael Elwell, along with Drs. Busey and Bolte, was convened on March 15, 2000, at HLS. EPA was invited to attend the PWG but decided not to send a representative.

The PWG examined all liver slides containing sections previously diagnosed by the SP or the PRP as indicating hepatocellular carcinoma, adenoma or non-neoplastic proliferative lesions of various degrees of severity (i.e., foci of cellular alteration and/or hypertrophy/ hyperplasia). All slides were coded so that the PWG was blinded to the treatment groups. The PWG diagnoses were unanimous with regard to every slide but one. The exception was that for one animal, one PWG pathologist believed that the liver contained a hepatocellular adenoma, while the other four believed it was an area of hepatocellular alteration (a non-neoplastic lesion). No changes in diagnoses were made after the slides were decoded. Cheminova submitted the PWG's report to EPA on March 20, 2000 (Hardisty, 2000).

The results of the PWG evaluation compared with the original diagnoses by the SP are shown below in Table 1. In that table, the SP tumor incidence values (percent) are expressed in two ways: 1) in terms of the total number of animals in each treatment group (as done by the PWG), and 2) in terms of the number of animals surviving at the time of appearance of the first tumor as presented in the CARC assessment (values in parentheses). Cheminova believes it is important to express the original malathion tumor incidence data in terms of the total number of animals per treatment group to allow proper comparison with the PWG data and with historical control data.

Table 1. Incidence of Liver Tumors in Female Rats Before and After PWG Review[a]

Tumor Type	Dose Levels (ppm)									
	0		100/50		500		6,000		12,000	
	SP	PWG	SP	PWG	SP	PWG	SP	PWG	SP	PWG
Number of Animals	70	70	55 (50)	55	55 (44)	55	55 (41)	55	70 (38)	70
Hepatocellular Adenoma	0	**0**	1	**1**	1	**2**	3	**0**	3	**5**
Hepatocellular Carcinoma	0	**0**	1	**0**	1	**0**	0	**0**	3	**0**
Combined	0	**0**	2	**1**	2	**2**	3	**0**	6	**5**
% Incidence	0%	**0%**	3.6% (4.0%)	**1.8%**	3.6% (4.5%)	**3.6%**	5.5% (7.3%)	**0%**	8.6% (16%)	**7.1%**

SP = Study pathologist result
PWG = PWG review result

[a] The SP tumor incidence values (percent) are expressed in terms of both the total number of animals in each treatment group and in terms of the number of animals surviving at the time of appearance of the first tumor (values in parentheses) as presented in the CARC assessment. See text for explanation.

The most significant changes in the diagnoses were as follows:

- The PWG concluded that there were no hepatocellular carcinomas at any dose level. All carcinomas originally diagnosed by the SP were diagnosed by the PWG as adenomas (i.e., non-malignant lesions).

- The PWG found that there were fewer adenomas than initially diagnosed by the study pathologist at doses below 12,000 ppm (1, 2, and 0 or 1.8%, 3.6%, and 0.0% in the 100/50, 500, and 6,000 ppm groups, respectively) and the PWG concluded that none of these were related to treatment. Furthermore, as shown in Table 2, the incidence of these tumors is well within the historical control range for the laboratory (0 to 5.4%) and for NTP (0 to 10%).

- At the highest dose level employed (12,000 ppm), the PWG concluded there were five adenomas, rather than with the three adenomas and three carcinomas originally identified by the SP.

Table 2. Historical Control Data (Hepatocellular Tumors in Female F344 Rats) [a]

Type of Tumor	NTP (n = 1900)		HLS (n = 254)	
	Mean	Range	Mean	Range
Hepatocellular Adenoma	2.3%	0-10%	1.6%	0-5.4%
Hepatocellular Carcinoma	0.2%	0-2%	1.1%	0-2.4%

a. Source: Haseman *et al*., 1990

2. Significance of PWG Conclusions

The PWG confirmed CARC's conclusion that the 12,000 ppm dose group is associated with excessive toxicity. Therefore, Cheminova believes that the tumors in the 12,000 ppm dose group should be disregarded for risk assessment purposes, as is EPA's normal practice.

The CARC classification of malathion as a "likely human carcinogen" is based primarily on the original diagnosis of liver tumors in female rats at doses that CARC did not consider excessive (i.e., below 12,000 ppm). Because the PWG determined that there were no carcinomas at any dose level, no adenomas in the 6,000 ppm dose group, and no adenomas related to treatment at the 500 ppm dose level and below, Cheminova believes that CARC now must reconsider its position.

B. CHEMINOVA'S CONCERNS ABOUT CARC'S ASSESSMENT OF MALATHION CHRONIC BIOASSAYS

Aside from the seminal new findings of the PWG, Cheminova has several serious concerns regarding CARC's assessment of the malathion carcinogenicity studies.

1. CARC's Position

Based on its review of the malathion chronic bioassay in the mouse (Slauter, 1994; MRID #43407201) and in the rat (Daly, 1996a; MRID #43942901), CARC concluded that:

- In rats, there is evidence of a treatment-related increased incidence of liver tumors only in females, and only at the two highest doses tested (6,000 and 12,000 ppm). In female rats, there was excessive toxicity at the 12,000 ppm level but not at the 6,000 ppm dose level, while in male rats there was excessive toxicity at both 12,000 ppm and 6,000 ppm.

- In the rat study, four benign nasal tumors were observed (one in each of the two highest dose levels in each sex). The only nasal tumor that occurred at a dose level not

considered to be associated with excessive toxicity was the one in female rats at 6,000 ppm. Nevertheless, CARC chose to attribute both nasal tumors occurring in female rats to treatment.

- In mice, there is evidence of a treatment-related increased incidence of liver tumors in both sexes but only at the two highest dose levels tested (8,000 and 16,000 ppm) where there was excessive toxicity.

- Malathion should be classified as a "likely human carcinogen" based primarily on the original diagnosis of liver tumors in female rats at a dose level (6,000 ppm) not considered by CARC to be excessive. CARC considered its classification to be supported by the increased incidence of liver tumors at high doses of malathion in mice and by the occurrence of the few (allegedly rare) nasal tumors in rats.

2. Cheminova's Position

a. Rat: Liver Tumors

The results from the chronic rat study (Daly, 1996a) are of critical importance because CARC's classification of malathion as a "likely human carcinogen" rests primarily on the three hepatic adenomas originally diagnosed in female rats fed 6,000 ppm malathion (Table 1). For female rats, CARC concluded that the high dose level (12,000 ppm) was excessive but that the 6,000 ppm dose level did not cause excessive toxicity. Since there was no significant increase in liver tumors at dietary dose levels of 50 or 500 ppm, the only tumors to achieve statistical significance at a dose level not considered by CARC to be excessive were the three adenomas in the 6,000 ppm female rats.

Cheminova does not agree with CARC's decision that the 6,000 ppm dose level in females was not excessive and can be used for risk assessment. While there was less mortality in the 6,000 ppm females than in males receiving the same dose level, blood and brain cholinesterases were inhibited to a substantial extent in both sexes. Given the long term duration and consistent degree of inhibition, there is no question that the animals of both sexes were under severe cholinergic stress. EPA's proposed Guidelines for Carcinogen Risk Assessment (July 1999) clearly indicate that "significant changes in clinical chemistry" can be considered as signs of treatment-related toxicity for purposes of risk assessment. Cheminova believes there was excessive cholinergic toxicity at 6,000 ppm and that the adenomas initially identified at this dose level should not have been used for risk assessment.

As it turns out, the results of the recent PWG review make CARC's concern about the results at the 6,000 ppm dose level irrelevant insofar as liver tumors are concerned. The PWG review confirms Cheminova's position that there is no evidence that malathion increases the incidence of liver tumors in rats, except at excessively toxic doses. This conclusion is strengthened by the failure to observe any increase in liver tumors in three earlier rat studies with malathion (see discussion below).

b. Rat: Nasal Tumors

In the chronic rat study, a total of four nasal epithelial cell tumors were observed, one in each of the two highest doses (12,000 and 6,000 ppm) of each sex; all were adenomas (Table 3). CARC noted that all but one of the tumors occurred at doses considered to be excessive, but nonetheless concluded that in females the tumors were treatment-related.

Table 3. Incidence of Nasal Tumors in the Malathion Chronic Rat Toxicity/Oncogenicity Study

Tumor Type	Dose Levels (ppm)				
	0	100/50	500	6,000	12,000
Females Nasal Epithelium Adenoma	0/90	0/90	0/90	1/90	1/90[a]
Males Nasal Epithelium Adenoma	0/90	0/90	0/90	1/90[a]	1/90[a]

[a] Incidences that CARC found occurred at doses causing excessive toxicity.

Cheminova believes that CARC should not have considered the nasal tumors as evidence of the potential carcinogenicity of malathion because:

- There is convincing evidence to support a localized, irritation effect resulting from prolonged, high level, exposure of the nasal epithelium as the mechanism explaining the nasal tumors. CARC has already characterized this mechanism as plausible. There is no evidence to support CARC's contention that the nasal tumors might arise through a systemic effect.

- All four of the tumors (in Cheminova's view) or all but one of the tumors (in CARC's view) occurred at dose levels that caused excessive cholinergic toxicity. Consequently, Cheminova does not believe that these tumors should be regarded as evidence of carcinogenicity or used for risk assessment purposes.

- While a localized irritation mechanism provides a plausible explanation of how malathion can cause nasal tumors in laboratory animals at high doses, it has no relevance to humans exposed intermittently to much lower doses of malathion under real world conditions.

- Cheminova disagrees with CARC's assertion that the tumors are so rare that, despite their lack of statistical significance, they should be regarded as evidence of carcinogenicity. The historical control data show that the tumors were well within the range of historical control incidence in 20 dietary NTP studies with rats of this strain.

i. All nasal tumors should be disregarded because they occurred at levels causing excessive toxicity.

All four of the tumors (in Cheminova's view) or all but one of the tumors (in CARC's view) occurred at dose levels that caused excessive cholinergic toxicity. Consequently, Cheminova does not believe that these tumors should be regarded as evidence of carcinogenicity or used in risk assessment, as is EPA's normal practice.

ii. Mechanism of nasal tumor formation

Cheminova believes that the nasal tumors were formed in response to prolonged, high level exposure of the nasal epithelium to malathion coming from the food as a vapor or adsorbed to inhaled food particles.

It is well-known that prolonged physical or chemical irritation, causing cytotoxicity and necrosis of the irritated tissue, will produce a state of reactive hyperplasia. Prolonged chemical-induced cell proliferation is a major causative factor in neoplasia because it decreases the capacity of the cell to repair damaged DNA and increases the probability of replicating the damaged DNA. Because all tissues contain initiated cells, cell proliferation can result in fixation of a spontaneous initiated event that would normally be repaired (Ames and Gold, 1990; Cohen and Ellwein, 1990).

For this reason, chemicals causing cell proliferation do not need to interact with DNA to induce neoplasia. This is recognized as a possible mechanism of cancer in EPA's draft Guidelines for Carcinogen Risk Assessment (July 1999) as follows:

> An increase in mutations might be due to cytotoxic exposures causing regenerative proliferation, or to mitogenic influences (Cohen and Ellwein, 1990). Increased cell division may elevate mutation by clonal expansion of initiated cells or by increasing the number of genetic errors by rapid cell division and reduced time for DNA repair.

Certainly, cell proliferation provides a plausible mechanistic explanation for the oncogenicity of many non-genotoxic chemicals and there are now several examples of chemicals known to induce cancer via this mechanism. These include the effects of chloroform and other compounds on liver (Larson *et al.*, 1994), butylated hydroxyanisole (BHA) and ethyl acrylate on the forestomach (Clayson *et al.*, 1990; Kroes *et al.*, 1986, Ghanayem *et al.*, 1991), and several chemicals on the thyroid (Hill *et al.*, 1989) and bladder (Swenberg, 1989).

Cheminova believes that there is ample evidence to suggest that induction of the occasional nasal tumor seen at the very high doses in the malathion study is mediated through a dose-related increase in non-neoplastic lesions. In the two recent chronic bioassays in both mice and rats (in which the same type of powdered feed was used), evaluation of the nasal tissues clearly showed an increased incidence of olfactory degeneration, atrophy and regenerative hyperplasia at the two highest dose levels that was not observed at lower doses (the CARC

statement to the contrary is incorrect; see the discussion on page 6 of these comments). The very few nasal tumors observed occurred only at these same high dose levels. Moreover, in shorter-term inhalation studies (2 and 13 weeks, MRIDs #44554301 and #43266601, respectively) with malathion, similar lesions of the nasal epithelium were described as being "indicative of an irritant effect on nasal and laryngeal mucosa". There is also evidence that cells in the respiratory and olfactory epithelium of rats contain high concentrations of the enzyme carboxylesterase that will metabolize malathion to the mono- and di-carboxylic acids. Similar acids are known to be irritants and cytotoxic agents that lead to the effects noted above (Bogdanffy, 1990; Bogdanffy *et al*., 1987; Olson *et al*., 1993).

CARC acknowledged the plausibility of the hypothesis that the nasal tumors observed at high doses were caused by an irritant effect, but chose to discount this hypothesis [emphasis added]:

> The Committee postulated that direct contact with malathion (by volatilization from the feed or by inhalation of the feed through the nose) was a plausible explanation for the nasal tumors. However, the committee concluded that *a systemic effect could not be unequivocally ruled out*. (EPA, 2000, p. vii).

The compelling evidence supports a localized irritation mechanism. Furthermore, the PWG determination that the liver tumors are not treatment related eliminates any support the liver tumors might have offered for a systemic mechanism. Therefore, Cheminova concludes that an irritation mechanism provides the only plausible explanation for the nasal tumors observed at high dose levels. Accordingly, these tumors should be regarded as unsuitable for dose-response extrapolation, as stated in EPA's July 1999 Draft Guidelines for Carcinogen Risk Assessment, Section 2.2.2.1, pages 2 to 12.

iii. Human Relevance

While this localized irritation mechanism provides a plausible explanation of how, at high doses, malathion can cause nasal turbinate tumors in laboratory animals, Cheminova wishes to emphasize that it has no relevance to humans exposed intermittently to much lower levels of malathion under real world conditions.

In considering the possible relevance of the rat nasal tumors to human risk assessment, it is also important to emphasize the general characteristics of tumors that occur via non-genotoxic mechanisms involving cell irritation and/or cytotoxicity:

- the tumors only occur following prolonged, high-level exposure to the chemical in question;

- tumor formation occurring as a result of non-neoplastic effects such as irritation and cytotoxicity is a **threshold-based effect** – i.e., there is a dose threshold below which tumor formation will not occur because the irritation and cytotoxicity does not occur; and

- preneoplastic and early neoplastic effects are likely to be fully reversible following cessation of exposure.

iv. Lack of statistical significance and the tumor rarity issue

The very low incidences of nasal tumors in the malathion study and their lack of statistical significance ordinarily would cause them to be disregarded for risk assessment purposes. However, CARC concluded that spontaneously occurring nasal tumors are "very rare" and therefore their occurrence is biologically significant, despite the fact that only a single tumor was observed in any given treatment group and there was no statistical significance.

Cheminova believes that the CARC conclusion about rarity was based on an inappropriate use of historical control data and a lack of information about the observed sectioning techniques employed.

In the HLS malathion study the incidence of olfactory and respiratory epithelial adenomas in both sexes is 1/90 (1.1%) at each of the two highest doses (6,000 and 12,000 ppm) for both males and females. It is true that these tumors were not observed in the concurrent control group, and exceed the laboratory's historical control range (0%). However, HLS had conducted only four other studies in the Fisher 344 rat before the malathion study, and has conducted no such studies after the malathion study. Moreover, only two sections per nasal tissue were evaluated in those four earlier studies, while in the malathion study five sections per nasal tissue were evaluated (as EPA required), thus increasing considerably the likelihood of a tumor diagnosis.

CARC states that the 1.1% incidence also exceeds the mean value for NTP historical control data as of 1996 (a total of 6 tumors out of a total of 4000 rats, or 0.0015%). Cheminova thinks the range is more appropriate to use than the mean.

Cheminova has obtained information on the range of values for nasal adenomas for 20 chronic dietary studies conducted by NTP during the years 1984 through 1996 studies (Analytical Sciences, 1999). As set forth in Table 4, the range was 0% to 2%. In one study a single male control rat had that type of tumor, and in another study a single female control rat had that type of tumor. Thus, in 2 of 20 studies (10% of the studies), there was a 2% incidence of the tumor in a control group. The NTP protocol used in these studies called for three sections per tissue type, more than in the standard HLS protocol but less than in the malathion study.

The incidences of nasal tumors for female rats from the malathion 24-month rat study are well within the historical control ranges shown in Table 4.

Table 4. Historical Control Data from 20 NTP Dietary Studies

Tumor type	Males		Females	
	Mean	Range	Mean	Range
Nose Adenoma[a]	0.1%	0-2% n = 1004	0.1%	0-2% n = 998

[a] Includes respiratory and olfactory adenoma (NTP does not distinguish between these)

The 20 NTP dietary studies involved 1,004 male and 998 female rats, so that the mean incidence for each sex is 0.1%. NTP also conducts studies using a variety of other routes of exposure. The NTP official responsible for maintaining these historical values is of the opinion that comparisons with historical control data are more appropriate when done by route of administration. In addition, in NTP studies, comparisons with historical control data are always made according to the route of administration employed. (Personal communication with Dr. Joseph Haseman, March 27, 2000).

c. Mouse Oncogenicity Study

Cheminova concurs with CARC's findings that in the mouse oncogenicity study (Slauter, 1994) there is an increased incidence of liver tumors (mainly adenomas) at the two highest dose levels employed (8,000 and 16,000 ppm). Cheminova also concurs with CARC's view that the two highest dose levels exceeded the Maximum Tolerated Dose (MTD). Indeed, the two high doses employed exceeded the EPA Limit Dose of 7,000 ppm and caused severe cholinergic toxicity**.** At all other doses (up to and including 800 ppm) it was concluded that there was no evidence of carcinogenicity in the liver or any other tissue. Cheminova thinks that the tumors observed at these excessively high dose levels should be disregarded for risk assessment purposes.

Cheminova concludes that, on the basis of this study and the earlier mouse study with malathion, there is no evidence of carcinogenicity in the mouse at levels below those causing excessive toxicity.

d. Other Studies Should be Taken into Account

CARC's evaluation focused almost entirely on the results of two studies conducted with malathion, an 18-month study in B6C3F1 mice (Slauter, 1994) and a 2-year study with Fischer 344 rats (Daly, 1996a); a 2-year rat study with malaoxon also received some attention (Daly, 1996b). CARC did not give any weight to the negative results in three earlier rat studies with malathion and one with malaoxon and two earlier mouse studies with malathion and malaoxon. While some of the earlier studies may have had some deficiencies, they still have value for assessing carcinogenicity and most of the malathion studies included high dietary dose levels of several thousand ppm. Cheminova believes that a proper weight-of-evidence evaluation should have considered the results of all available studies.

In view of the recent PWG findings, there is no evidence, in any of the nine studies available, of a treatment-related, statistically significant increase in any tumor type at dose levels that were not considered excessive. The available studies are:

For Malathion:

- 18 month oral oncogenicity study in mice (Slauter, 1994)
- 24 month oral toxicity/oncogenicity study in F 344 rats (Daly, 1996a)
- 24 month oral toxicity/oncogenicity study in S-D rats (Rucci et al, 1980)
- 18 month oral carcinogenicity/chronic toxicity study in mice (NCI, 1978a)
- 24 month oral carcinogenicity/chronic toxicity study in O-M rats (NCI, 1978b)
- 24 month oral carcinogenicity/chronic toxicity study in F 344 rats (NCI 1979a)

For Malaoxon:

- 24 month oral toxicity/oncogenicity study in F 344 rats (Daly et al, 1996b)
- 24 month oral toxicity/oncogenicity study in F 344 rats (NCI, 1978c)
- 18 month oral carcinogenicity/ chronic toxicity study in mice (NCI, 1979b)

C. CHEMINOVA'S CONCERNS ABOUT CARC'S GENOTOXICITY ASSESSMENT

1. CARC's Conclusion

CARC concedes that the guideline studies indicate that malathion is not genotoxic. However, CARC states that "while the evidence for mutagenicity as an influence on the carcinogenicity of malathion is weak, at this time it can not be ruled out" (EPA, 2000, pg vii). The latter caveat is based entirely on the results of non-guideline studies and an allegation that the structure of malathion suggests that it might be an electrophilic alkylating agent.

2. Cheminova's Comments

Cheminova believes that the total weight of evidence overwhelmingly shows that malathion is negative for genotoxicity. Cheminova does not agree that the studies from the open literature confirm malathion to be a mutagen or clastogen or that the structure of malathion suggests that it might be an electrophilic alkylating agent. Moreover, Cheminova believes that much greater weight should have been given to the guideline studies, which are uniformly negative. Each of these points is discussed below.

a. <u>Guideline Studies Show that Malathion is not Mutagenic or Clastogenic</u>

Cheminova believes the guideline studies are reliable and sufficient to evaluate the mutagenicity of malathion. Cheminova agrees with CARC that the results of the guideline studies with malathion are negative:

> Results of the guideline genetic toxicology studies with malathion indicate that the test material did not cause gene mutations in bacteria or UDS in cultured rat hepatocytes. Similarly, malathion was neither clastogenic nor aneugenic up to doses that showed clear cytotoxicity for the target tissue *in vivo*. (EPA, 2000, pg. 33)

b. Studies from the Open Literature Cited by CARC Need Further Evaluation

In its report, CARC goes as far as to state that there is "*overwhelming* confirmation from the published literature demonstrating that malathion is genotoxic…." However, elsewhere it concedes that in 5 out of 7 reportedly "positive" *in vivo* bone marrow studies and in 5 out of 6 "positive" *in vitro* cytogenetic studies, the doses used were cytotoxic. Findings at cytotoxic doses are usually excluded from genotoxicity evaluations.

In reaching its conclusion about the mutagenicity/clastogenicity of malathion, it appears that CARC relied solely on the Flessel *et al*. (1993) review article and not on the primary references. EPA does not discuss whether it considered weaknesses often seen in published studies, including lack of GLP compliance, lack of dose concentration or homogeneity analyses, lack of characterization of the test substance purity, absence of individual animal data, and insufficient reporting of methodology and results. The merits of each of the published non-guideline studies need to be carefully examined, based on a review of the primary reference, to determine the adequacy of the study and what weight, if any, should be given to the study results.

When considering the results of the mutagenicity/clastogenicity studies reported in the open literature (Flessel *et al*., 1993), it is important to consider several factors such as the dose levels as well as the source and purity of the malathion employed. A variety of sources and purities (30 to >99%) of malathion have been tested in genotoxicity assays and the results reported in the open literature. Flessel *et al*. (1993) concluded that some of the positive results of these studies could be due to the impurities found in the malathion tested, and not directly to malathion itself.

c. Electrophilicity Issue is Irrelevant

On the issue of electrophilicity, Cheminova believes that the primary reference (Ashby and Tennant, 1988), on which CARC's conclusion was based, was misstated and misused by CARC. Ashby and Tennant's work was simply an attempt to identify certain structural groups as "alerts" for possible mutagenicity in the absence of any other data (i.e., with untested chemicals). They did not intend that their suggested "alerts" should be used in a weight-of-the-evidence evaluation or be given the same weight as actual data. (Personal communication with Dr. John Ashby, March 2000.)

While methyl groups in some structures are reactive electrophiles that justify an alert as possible alkylating agents, this is not true for the methyl groups of alkyl phosphate esters

(and their thio analogs). In fact, the methyl groups in malathion are quite stable, unreactive moieties and are highly unlikely to be alkylating agents. Indeed, it is instructive to review the data in Table 10 of the Ashby and Tennant paper. The data for 15 alkyl phosphates (the class of compounds to which malathion belongs) clearly show the lack of any convincing correlation among structure, mutagenicity, and carcinogenicity.

The last sentence in the legend to Table 10 states that "the correlation between chemical structure, mutagenicity to *Salmonella* and rodent carcinogenicity is poor for this class of compounds." Furthermore, in the text of the paper, the authors emphasize that "For these agents [the alkylphosphoric acid esters] there appear to be no useful correlations evident between S/A [structure activity], mutagenicity or carcinogenicity" (Ashby and Tennant, 1988). Cheminova, therefore, believes that CARC misstates the data in the Ashby and Tennant paper and requests that all reference to the electrophilicity of malathion in the context of genotoxicity be removed from the CARC report and EPA's risk assessment.

D. EPIDEMIOLOGY

A study on the mortality and incidence of cancer among employees at Cheminova was conducted by the Danish Institute for Clinical Epidemiology and the Danish Cancer Society at the request of Cheminova's Works and Safety Council (Juel & Lynge, 1995). (Cheminova is submitting this report to EPA along with these comments.) All staff who had been employed for at least one year at Cheminova during the period 1953 to 1993 were included in the survey. In all, the survey included 1,467 people, composed of 1,275 men and 192 women. Among the 1,467 persons, there were 158 deaths among men and two among women through December 31, 1993. The deaths among men were distributed as follows: cancer (27%), cardiovascular disease (47%), other natural causes (16%) and accidents and suicides (10%). The causes of four deaths were unknown.

Mortality among male employees was at a level equivalent to that of the general Danish population. The group which was assessed as having had a low exposure to organophosphorus compounds during their period of employment had a slightly lower mortality than a group considered to have had a higher level of exposure. However, the differences were no larger than those normally observed between white- and blue-collar workers. Analysis of mortality due to specific causes revealed no significant differences between Cheminova workers and the general population of Denmark. Mortality among women did not deviate from that expected.

During the entire study period, 84 new cases of cancer occurred among men and three among women. For men, the number of new cancer cases corresponded to the expected number based on the incidence of cancer in the Danish population as a whole. Lung cancer, cancer of the bladder and normal skin cancer accounted for the majority of cases, totaling 20, 10 and 10 respectively. For all three groups, the observed number of cases was close to that expected in the general population of Denmark. There was no incidence of cancer of the liver, no incidence of cancer of the nose, and 1 incidence of cancer of the throat (1.67 were expected). The only unusual finding noted was that there were 2 cases of cancer of the saliva

gland, where only 0.21 were expected. However, as the report states: "with such small numbers it is difficult to form conclusions." The incidence of cancer among women did not deviate from the expected pattern. In conclusion, the surveys demonstrated no increased mortality or increased incidence of cancer among employees at Cheminova.

E. CHEMINOVA'S CONCLUSION ON THE WEIGHT OF EVIDENCE REGARDING THE CARCINOGENICITY CLASSIFICATION OF MALATHION

Cheminova concludes the following:

- CARC's classification of malathion as a "likely human carcinogen" was based primarily on the original diagnosis of liver tumors in female rats at dose levels that were not considered excessive (i.e., below 12,000 ppm). The fact that the PWG did not find carcinomas at any dose level, combined with the PWG conclusions that there were only three adenomas at dose levels up to and including 6,000 ppm (0 at 6,000 ppm) and that these were not treatment related, obviates the principal rationale for CARC's position.

- CARC should not consider the nasal tumors as evidence for carcinogenicity, in view of the historical control information showing that these tumors are not rare and the compelling evidence showing that these tumors are caused by a localized, high-dose irritation mechanism not relevant to human risk assessment.

- The total weight of evidence clearly indicates that malathion is not mutagenic or clastogenic. The guideline studies are entitled to the greatest weight, and they are uniformly negative. CARC's proposed use of selected published non-guideline studies to support a position that malathion might be genotoxic is unjustified and inappropriate. Most of the allegedly positive results came from dose levels that were cytotoxic and thus should have been ignored. Moreover, there is no indication that CARC has conducted a careful evaluation of the quality and validity of these non-guideline studies.

- Cheminova's epidemiological data do not indicate that workers exposed to malathion have any greater risk of mortality, morbidity, or cancer than members of the general population.

- The new PWG findings alone require CARC to reconsider its classification of malathion as a "likely human carcinogen." The only scientifically supportable classification of malathion is "unlikely to be carcinogenic to humans." As such, calculation of a Q_1* is inappropriate.

IV. TOXICOLOGY AND ENDPOINTS FOR THE RISK ASSESSMENTS

A. FQPA SAFETY FACTOR

Cheminova agrees with EPA that the existing data do not indicate any special sensitivity of malathion to children; therefore, the Food Quality Protection Act (FQPA) 10x safety factor should be removed.

B. TOXICITY ENDPOINTS FOR THE ACUTE DIETARY RISK ASSESSMENT

Cheminova will soon submit the results from a recent human volunteer study that demonstrated a NOEL for RBC and plasma cholinesterase inhibition and for adverse events of 15 mg/kg body weight (the highest dose tested). Cheminova believes that the results from this study provide useful information for setting an appropriate NOEL for use in the acute dietary risk assessment for malathion.

C. TOXICITY ENDPOINTS FOR THE CHRONIC DIETARY RISK ASSESSMENT

The chronic reference dose (RfD) that was calculated in the 1997 HIARC document was based on the chronic NOAEL corresponding to 4 mg/kg/day (100/50 ppm). This number has been revised to 2.4 mg/kg/day. EPA's recalculations involved assessment of mean dietary intake of malathion for the low dose group from weeks 18 through 102 (when the dose level was decreased from 100 ppm to 50 ppm because of RBC cholinesterase inhibition at the 3-month interval). Cheminova confirmed EPA's calculations.

EPA has also recalculated mean test substance intake for all other dose groups and has presented them on page 3 of the "Revised NOAEL for Chronic RfD" document. EPA's revised numbers are approximately 10% lower than those calculated by the laboratory. Cheminova was not able to reproduce EPA's calculations. Cheminova requests that EPA provide an explanation of how it has recalculated these numbers.

D. TOXICITY ENDPOINT FOR THE SHORT-TERM INHALATION EXPOSURE RISK ASSESSMENT

Cheminova disagrees with EPA's use of a lowest-observed-adverse effect level (LOAEL) of 0.1 mg/L from the 90-day rat inhalation study for assessing short-term inhalation exposure risks for the following reasons:

- Cheminova believes that that the 0.1 mg/L value from the 90-day inhalation study is a NOAEL rather than a LOAEL (see Section IV.I.2). Based on statistically significant inhibition of plasma, RBC, and brain ChE activities at doses greater than 0.1 mg/L, 0.1 mg/L is a clear NOEL in this study.

- The results from a 90-day inhalation study are not appropriate for assessing potential risks from short-term (defined by EPA as 1 to 7 days) inhalation exposure. Cheminova believes that data from a study with exposure duration of up to 7 days would be more appropriate for this risk assessment.

However, in light of the histopathological findings occurring in the 90-day inhalation toxicity study at and above the lowest dose level and the absence of a short-term NOEL, Cheminova is considering conducting new studies, using a tiered approach.

E. TOXICITY ENDPOINT FOR THE INTERMEDIATE-TERM DERMAL EXPOSURE RISK ASSESSMENT

At this time, Cheminova has no comments regarding the endpoint chosen by EPA for this risk assessment.

F. TOXICITY ENDPOINT FOR THE INTERMEDIATE-TERM INHALATION EXPOSURE RISK ASSESSMENT

EPA is using what it considers to be the LOAEL from the 90-day inhalation toxicity study (0.1 mg/L), with a 10x-uncertainty factor, to assess potential risks for intermediate-term inhalation exposure. As mentioned before, Cheminova believes a clear NOAEL of 0.1 mg/L for plasma, RBC, and brain ChE inhibition was established in this study. However, in light of the histopathological findings occurring in this study at and above the lowest dose level, Cheminova is considering conducting new studies, using a tiered approach.

G. TOXICITY ENDPOINT FOR THE LONG-TERM DERMAL EXPOSURE RISK ASSESSMENT

At this time, Cheminova has no comments regarding the endpoint chosen by EPA for this risk assessment.

H. TOXICITY ENDPOINT FOR THE LONG-TERM INHALATION EXPOSURE RISK ASSESSMENT

EPA is using what they consider to be the LOAEL from the 90-day inhalation toxicity study (0.1 mg/L), with a 10x-uncertainty factor, to assess potential risks for long-term inhalation exposure. As mentioned before, Cheminova believes a clear NOAEL of 0.1 mg/L for plasma, RBC, and brain ChE inhibition was established in this study. However, in light of the histopathological findings occurring in this study at and above the lowest dose level, Cheminova is considering conducting new studies, using a tiered approach.

I. TOXICOLOGY DATA REQUIREMENTS

1. 90-Day Dog Toxicity Study

In its Hazard Profile, Section 3.1, EPA is requiring a 90-day feeding study in dogs because the available 1-year study is unacceptable. EPA classified the 1-year study as core-supplemental mainly because a NOEL for cholinesterase inhibition was not identified.

Cheminova believes that a 90-day feeding study in dogs in not needed because available data from a 1-year dog toxicity study (using 6 animals/sex/group) and a 28-day dog toxicity study (using 3 animals/sex/group) provide adequate information on the toxicity of malathion in non-rodent species. Each of these studies is discussed below.

- In the 1-year dog study, Cheminova believes that the NOEL is 62.5 mg/kg bw/day based on statistically significant inhibition of plasma and RBC cholinesterase activity at the next higher dose level.

- With these comments, Cheminova is submitting a final report for a 28-day oral toxicity study of malathion (92.4%) in Beagle dogs (Fischer, 1988). In this study, 3 dogs/sex/group were given 0, 125, 250, or 500 mg malathion/kg bw/day by capsule daily for 28 days. One dog died at 500 mg/kg bw/day (became listless and anorexic). Clinical signs (diarrhea and loose and mucoid stool), decreased food consumption, and statistically significant body weight gain were seen at 500 mg/kg bw/day. At 250 and 125 mg/kg bw/day, no significant effects were noted on food intake, body weight gain, organ weights, clinical chemistry and hematological parameters. No microscopic changes were seen in any of the tissues examined at any of the dose levels tested. Cholinesterase data indicate statistically significant inhibition of plasma and RBC cholinesterase activities at 250 and 500 mg/kg bw/day. Based on statistically significant inhibition of plasma and RBC cholinesterase activity, the NOEL is 125 mg/kg bw/day.

Cheminova believes that the data provided in these two studies should be sufficient for characterizing the toxicity of malathion in non-rodent species. Conducting an additional 90-day feeding study in dogs will provide no data that would alter the present dietary and non-dietary risk assessments.

2. 90-Day Inhalation Rat Toxicity Study

In its Hazard Profile, Section 3.1, EPA stated that it is requiring a new 90-day inhalation study in rats because the available 90-day study did not establish a NOEL.

Cheminova believes that the submitted study did establish a NOEL for plasma, RBC, and brain cholinesterase inhibition. In the 90-day rat inhalation study, a clear NOAEL was established for plasma, RBC, and brain cholinesterase inhibition at 0.1 mg/L for males and

females (see Table 5 below). The data show that cholinesterase inhibition in all three compartments at 0.1 mg/L is neither greater than 20% nor statistically significant.

Table 5. A 90-Day Inhalation Study in Rats—Cholinesterase Data (% Inhibition)

Cholinesterase	Males			Females		
	Dose levels (mg/L)			Dose levels (mg/L)		
	0.1	0.45	2.0	0.1	0.45	2.0
Plasma	2.1	7.2	18.3	16.4	29.6	69.6***
RBC	8.9	22.2*	42.7**	10.6	26.5*	44.2**
Brain	4.6	2.7	17.0**	4.5	7.9	41.3**

*p<0.05, **p<0.01, ***p<0.001

Cheminova believes that if new data are necessary, a tiered approach to the testing will be most appropriate.

V. SUPPORTED USE PATTERNS FOR MALATHION

Cheminova has reviewed the use information that EPA included in its risk assessments. In general, Cheminova believes that EPA has accurately summarized the uses and use patterns that will be supported in reregistration.

A. GOVERNMENT PROGRAMS

Cheminova believes it is not appropriate for EPA to extrapolate potential risks from exposures associated with government-sponsored programs, such as the boll weevil eradication program, the MedFly eradication program, and the public health use of malathion for adult mosquito control, to potential risks from typical agricultural use of malathion. Cheminova's opinion is based on the following:

- the use of malathion for these government-sponsored programs is often temporary;
- the programs are often highly localized, and may not be representative of conditions in other areas; and
- the use patterns for these programs are very different from typical agricultural uses of malathion.

Cheminova believes that separate risk assessments for these programs should be conducted and presented separately from typical agricultural uses of malathion.

B. MALATHION REGISTRATIONS

1. Technical Registrations

On page 6 of its draft chapter, EFED claims that all of the technical malathion produced in the United States is manufactured, marketed, and distributed by Cheminova. Cheminova notes that EPA recently granted a new registration of technical malathion to Griffin L.L.C. In addition, technical product registrations are held by Prentiss, Inc., Verdant Brands, Inc., AMVAC Chemical Corp., Gowan Chemical Company, Drexel Chemical Company, Platte Chemical Company, Inc., and Micro-Flo Corporation.

Because Cheminova is the only submitter of generic data, its decisions regarding supported uses of malathion should be regarded as applicable to all other registrations, unless other registrants are willing to develop their own data to support their registrations.

2. Registered End-Use Products

As stated in its March 10, 1998, letter responding to EPA's February 17, 1998, memorandum regarding supported uses, Cheminova is supporting only the following formulations of malathion:

- Emulsifiable Concentrates (EC);
- Ultra Low Volume (ULV);
- Dusts;
- Ready To Use (RTU); and
- Wettable Powders (WP).

No other formulation type should be included in the Agency's risk assessments.

Regarding malathion dust formulations, Cheminova notes that it is supporting the use of this formulation only for certain agricultural uses (dates and stored grains). Cheminova is not supporting malathion dust formulations for non-agricultural and residential uses.

3. FIFRA Section 24(c) Registrations

NPIRS lists a total of 27 malathion registrations under FIFRA section 24(c). Cheminova is supporting only the section 24(c) registrations that are covered by the food/feed use patterns that it is supporting for reregistration, which are identified below; only these registrations and registrations supported by IR-4 should be considered in the Agency's risk assessments. Cheminova recommends that the Agency determine whether any of the unsupported registrations are still active at the state level and whether the registrants have paid maintenance fees.

C. Supported Food/Feed Uses and Use Patterns

At this time, Cheminova is supporting the use patterns identified in Tables 6 through 10 for reregistration. These proposed use patterns are based on the residue data that have been submitted to the Agency. Cheminova will be discussing with grower groups the adequacy of these proposed use rates as well as how malathion is typically used in the field. We encourage the Agency to hold similar discussions. These discussions may identify changes to one or more parameters defining the use patterns for these crops (e.g., maximum single application rate, maximum number of applications per year, application interval, etc.).

The tables in EPA's documents do not clearly present the use patterns that Cheminova intends to support for reregistration. Cheminova recommends that EPA include tables similar to the following tables in its documents.

Table 6. Malathion: Proposed Use Patterns for the EC Formulations [a]

Supported Crop [b]	Maximum Single Application Rate (1b a.i./A)	Maximum Number of Applications per Year	Minimum Application Interval (days)	Minimum Pre-Harvest Interval (days)
Alfalfa	1.25	2	14	0
Apple	*1.25*	*5*	*7*	*3*
Apricots	*3.75*	*4*	*7*	*6*
Asparagus	*1.25*	*9*	*7*	*1*
Avocado	4.70	2	30	7
Barley	1.25	3	7	7
Beets, garden	1.25	5	7	7
Blackberry	*2.0*	*4*	*7*	*1*
Boysenberry	*2.0*	*4*	*7*	*1*
Broccoli	*1.25*	*5*	*7*	*2*
Broccoli raab	*1.25*	*5*	*7*	*2*
Brussels sprouts	*1.25*	*5*	*7*	*2*
Cabbage	*1.25*	*10*	*7*	*7*
Carrot	1.25	7	7	7
Cantaloupe	*1.0*	*6*	*7*	*1*
Cauliflower	*1.25*	*5*	*7*	*2*
Celery	*1.5*	*3*	*7*	*7*
Chayote root	1.50	2	7	0
Chayote fruit	1.88	3	7	1

a. Note: *Italics—data submitted by IR-4* Normal case—data submitted by Cheminova

b. Based on Cheminova's March 10, 1998, letter clarifying the supported uses for malathion.

Table 6. Malathion: Proposed Use Patterns for the EC Formulations (continued) [a]

Supported Crop [b]	Maximum Single Application Rate (1b a.i./A)	Maximum Number of Applications per Year	Minimum Application Interval (days)	Minimum Pre-Harvest Interval (days)
Cherries (sweet)	8	6	7	3
Cherries (tart)	3.75	6	7	3
Chestnut	*5.0*	*4*	*7*	*2*
Clover	1.25	2	14	0
Collards	*1.25*	*6*	*7*	*3*
Corn, field	1.25	3	7	7
Corn, sweet	1.25	5	5	5
Corn, pop	1.25	3	7	7
Cotton	2.50	25	3	0
Cucumber	1.88	3	7	1
Dandelion	*2.0*	*3*	*7*	*7*
Dewberry	1.25	4	4	1
Eggplant	3.50	5	5	3
Endive (escarole)	1.88	6	5	14
Fig	*2.5*	*3*	*5*	*5*
Flax	*0.5*	*1*	*0*	*52*
Garlic	1.5	5	7	3
Grapefruit	6.25	3	30	7
Grapes	1.88	2	14	3
Grasses (forage an hay)	1.25	1	n/a	0
Guava	*1.25*	*13*	*7*	*2*
Hops	*1.25*	*2*	*?*	*10*
Horseradish	*1.25*	*5*	*7*	*7*
Kale	*1.25*	*6*	*7*	*3*
Kohlrabi	*1.25*	*5*	*7*	*2*
Kumquat	6.25	3	30	7
Leeks	1.5	5	7	3
Lemon	6.25	3	30	7
Lespedeza	1.25	2	14	0
Lettuce, head	1.88	6	5	14
Lettuce, leaf	1.88	6	5	7
Lime	6.25	3	30	7
Loganberry	*2.0*	*4*	*7*	*1*
Lupine	1.25	2	14	0

a. Note: *Italics—data submitted by IR-4*, Normal case—data submitted by Cheminova.
b. Based on Cheminova's March 10, 1998, letter clarifying the supported uses for malathion.

Table 6. Malathion: Proposed Use Patterns for the EC Formulations (continued) [a]

Supported Crop [b]	Maximum Single Application Rate (1b a.i./A)	Maximum Number of Applications per Year	Minimum Application Interval (days)	Minimum Pre-Harvest Interval (days)
Macadamia nut	*0.94*	*7*	*7*	*1*
Mango	*1.25*	*8*	*7*	*1*
Melon	*1.0*	*6*	*7*	*1*
Mint	*0.94*	*3*	*7*	*7*
Mushroom	*1.70*	*4*	*4*	*1*
Mustard greens	*1.25*	*6*	*7*	*3*
Nectarines	*3.75*	*4*	*7*	*6*
Oats	1.25	3	7	7
Okra	*1.5*	*6*	*7*	*1*
Onions (bulb & green)	1.5	5	7	3
Orange	6.25	3	30	7
Papaya	*1.25*	*13*	*7*	*1*
Parsley	*2.0*	*3*	*7*	*7*
Parsnip	*1.25*	*5*	*7*	*7*
Passion fruit	1.25	8	7	3
Peach	*3.75*	*4*	*14*	*7*
Pear	*1.25*	*5*	*7*	*1*
Peas, dried	*2.5*	*5*	*7*	*2*
Peas, succulent	*2.5*	*5*	*7*	*2*
Pecans	*2.5*	*3*	*7*	*7*
Peppers	1.50	5	5	3
Pineapples	*5.0*	*3*	*6*	*7*
Potatoes	1.50	2	7	0
Pumpkin	*1.0*	*6*	*7*	*1*
Quince	*1.25*	*5*	*7*	*3*
Radish	*1.25*	*5*	*7*	*7*
Raspberry	*2.0*	*4*	*7*	*1*
Rice	1.25	3	7	7
Rutabaga	*1.25*	*5*	*7*	*7*
Rye	1.25	3	7	7
Salsify	*1.25*	*5*	*7*	*7*
Shallots	1.5	5	7	3
Sorghum grain	1.25	3	7	7
Spinach	*2.0*	*3*	*7*	*7*

a. Note: *Italics—data submitted by IR-4,* Normal case—data submitted by Cheminova

b. Based on Cheminova's March 10, 1998, letter clarifying the supported uses for malathion.

Table 6. Malathion: Proposed Use Patterns for the EC Formulations (continued) [a]

Supported Crop [b]	Maximum Single Application Rate (1b a.i./A)	Maximum Number of Applications per Year	Minimum Application Interval (days)	Minimum Pre-Harvest Interval (days)
Squash (summer)	1.88	3	7	1
Squash (winter)	*1.0*	*6*	*7*	*1*
Strawberry	*1.88*	*6*	*7*	*3*
Sweet potatoes	1.50	2	7	0
Swiss chard	*2.0*	*3*	*7*	*7*
Tangelo	6.25	3	30	7
Tangerines	6.25	3	30	7
Tomato (including tomatillo)	3.50	5	5	3
Turnip	*1.25*	*5*	*7*	*7*
Vetch	1.25	2	14	0
Walnuts	*2.5*	*3*	*7*	*7*
Watercress	*1.25*	*5*	*5*	*3*
Watermelon	*1.0*	*6*	*7*	*1*
Wheat, spring	1.25	3	7	7
Wheat, winter	1.25	3	7	7
Wild rice	1.25	3	7	7
Yams	1.50	2	7	0

a. Note: *Italics—data submitted by IR-4,* Normal case—data submitted by Cheminova
b. Based on Cheminova's March 10, 1998, letter clarifying the supported uses for malathion.

Table 7. Malathion: Proposed Use Patterns for the ULV Formulations [a]

Supported Crop [b]	Maximum Single Application Rate (1b a.i./A)	Maximum Number of Applications per Year	Minimum Application Interval (days)	Minimum Pre-Harvest Interval (days)
Alfalfa	0.61	2	14	0
Barley	0.61	3	7	7
Beans, dry	0.61	3	7	1
Beans, succulent	0.61	3	7	1
Cherries (sweet)	1.22	6	7	1
Cherries (tart)	1.22	6	7	1
Clover	0.61	2	14	0

a. Note: *Italics—data submitted by IR-4,* Normal case—data submitted by Cheminova
b. Based on Cheminova's March 10, 1998, letter clarifying the supported uses for malathion.

Table 7. Malathion: Proposed Use Patterns for the ULV Formulations (continued) [a]

Supported Crop [b]	Maximum Single Application Rate (1b a.i./A)	Maximum Number of Applications per Year	Minimum Application Interval (days)	Minimum Pre-Harvest Interval (days)
Corn, field	0.61	3	7	7
Corn, sweet	0.61	5	5	5
Corn, pop	0.61	3	7	0
Cotton	1.22	25	3	0
Grapefruit	*0.92*	*4*	*5*	*1*
Grasses (hay grass)	0.92	1	n/a	0
Kumquat	*0.92*	*4*	*5*	*1*
Lemon	*0.92*	*4*	*5*	*1*
Lespedeza	0.61	2	14	0
Lime	*0.92*	*4*	*5*	*1*
Lupine	0.61	2	14	0
Oats	0.61	3	7	7
Orange	*0.92*	*4*	*5*	*1*
Orange	0.18	10	7	1
Rice	0.61	3	7	7
Rye	0.61	3	7	7
Sorghum grain	0.61	3	7	7
Tangelo	*0.92*	*4*	*5*	*1*
Tangerine	*0.92*	*4*	*5*	*1*
Vetch	0.61	2	14	0
Wheat, spring	0.61	3	7	7
Wheat, winter	0.61	3	7	7
Wild rice	0.61	3	7	7

a. Note: *Italics—data submitted by IR-4,* Normal case—data submitted by Cheminova
b. Based on Cheminova's March 10, 1998, letter clarifying the supported uses for malathion.

Table 8. Malathion: Proposed Use Patterns for the Dust Formulations [a]

Supported Crop [b]	Maximum Single Application Rate (1b a.i./A)	Maximum Number of Applications per Year	Minimum Application Interval (days)	Minimum Pre-Harvest Interval (days)
Dates	4.25	5	13	7
Stored barley [c]	Loading: 0.62 lb/1000 bushels Storage: 0.31 lb/1000 bushels	3	60	n/a
Stored corn [c]	Loading: 0.62 lb/1000 bushels Storage: 0.31 lb/1000 bushels	3	60	n/a
Stored oats [c]	Loading: 0.62 lb/1000 bushels Storage: 0.31 lb/1000 bushels	3	60	n/a
Stored rye [c]	Loading: 0.62 lbs/1000 bushels Storage: 0.31 lb/1000 bushels	3	60	n/a
Stored wheat [c]	Loading: 0.62 lbs/1000 bushels Storage: 0.31 lb/1000 bushels	3	60	n/a

a. Note: *Italics—data submitted by IR-4,* Normal case—data submitted by Cheminova.
b. Based on Cheminova's March 10, 1998, letter clarifying the supported uses for malathion.
c. One application of 57 EC was made to the inside of the empty grain bin prior to treatment of the grain with the dust formulation.

Table 9. Malathion: Proposed Use Patterns for the RTU Formulations [a]

Supported Crop [b]	Maximum Single Application Rate (1b a.i./A)	Maximum Number of Applications per Year	Minimum Application Interval (days)	Minimum Pre-Harvest Interval (days)
Cotton	1.15	25	3	0

a. Based on submitted residue data.
b. Based on Cheminova's March 10, 1998, letter clarifying the supported uses for malathion.

Table 10. Malathion: Proposed Use Patterns for the WP Formulations [a]

Supported Crop [b]	Maximum Single Application Rate (1b a.i./A)	Maximum Number of Applications per Year	Minimum Application Interval (days)	Minimum Pre-Harvest Interval (days)
Blackberry	*2.0*	*4*	*7*	*1*
Boysenberry	*2.0*	*4*	*7*	*1*
Dewberry	*2.0*	*4*	*7*	*1*
Loganberry	*2.0*	*4*	*7*	*1*
Raspberry	*2.0*	*4*	*7*	*1*
Strawberry	*2.0*	*6*	*7*	*3*

a. Note: IR-4 submitted the residue data to support the use of malathion on these crops.
b. Based on Cheminova's March 10, 1998, letter clarifying the supported uses for malathion.

D. SUPPORTED NON-FOOD/FEED USES AND USE PATTERNS

As stated in Cheminova's March 10, 1998, letter, the following non-agricultural uses will not be supported for reregistration:

- homeowner lawns;
- ornamental lawns and turf; and
- golf course turf.

In addition, there are some non-food/feed uses that are currently allowed by Cheminova's technical label that Cheminova will not continue to support. The list of these uses can be found in EPA's February 17, 1998, memorandum. Cheminova will remove these unsupported uses from its label in response to a requirement in the final Reregistration Eligibility Decision (RED) document for malathion.

E. MALATHION LABELS

As the primary registrant that has submitted the generic data to support malathion registrations, Cheminova agrees with HED's recommendation (page 3 of the April 14, 1999, draft Residue Chemistry Science Chapter) that following the issuance of the final RED, EPA must require all malathion registrants to amend their end-use product labels to make them consistent with the basic producer label. Cheminova is willing to assume a leadership role in working with EPA and the end-use registrants to make these revisions.

VI. DIETARY EXPOSURE RISK ASSESSMENTS

EPA's acute and chronic dietary risk assessments, based on conservative assumptions and estimated residues, show that there is no concern resulting from acute or chronic exposure to estimated malathion residues in food. Cheminova notes, however, that further refinements to the dietary risk assessments will be possible using data from the Organophosphate Market Basket Survey (OPMBS). A final OPMBS report should be available to the Agency in mid-2000. Cheminova requests that the Agency use these data to further refine the dietary risk assessments for malathion.

VII. RESPONSE TO EFED'S SELECTION OF DRINKING WATER CONCENTRATIONS

A. BACKGROUND

EFED estimated drinking water concentrations from surface water bodies and groundwater. For surface waters, EFED used the Tier I runoff model GENEEC to estimate an acute malathion concentration of 226.0 ppb, and an acute malaoxon concentration of 96.0 ppb. EFED used the 56-day GENEEC values to estimate a chronic malathion concentration of 21.2 ppb, and a chronic malaoxon concentration of 75.5 ppb. The GENEEC model estimates water concentrations in a 1-hectare farm pond, assuming that runoff from a 10-hectare field drains into the farm pond and spray drift from 1 hectare of the field falls into the pond.

Initially, EFED ran the conservative, screening-level groundwater model, SCI-GROW, to estimate groundwater concentrations. However, the highest concentration was 0.142 ppb for cotton, which was lower than a few monitoring measurements in EPA's Pesticides in Groundwater Database. Therefore, EFED decided to use a high-end value of 3.1 ppb for malathion from EPA's Pesticides in Groundwater Database. EPA assumed that malaoxon concentrations were identical to malathion. This value was assumed for both acute and chronic exposure.

B. CHEMINOVA'S RESPONSE

Cheminova believes that EPA should not rely on the highly conservative GENEEC model or the Pesticides in Groundwater Database for drinking water concentrations. GENEEC provides a highly conservative estimate of water concentrations in a static farm pond. This does not represent a drinking water source. Additionally, there are serious questions about the validity of some of the measurements that EFED has relied upon in the Pesticides in Groundwater Database, which is a collection of measurements made from 1971 through 1991 from a variety of sources. These concerns were discussed in a report sent to EPA in December of 1993 by Cheminova entitled "Overview of the Environmental Behavior of Malathion and Response to EPA's Reviews of Malathion Environmental Fate Studies" (Severn, 1993, MRID 43166301).

Instead, EPA should rely on the extensive monitoring data that have been collected since the early 1990s with advanced analytical methods. The two major databases are as follows:

- A recent report co-sponsored by Cheminova that reviewed available data for finished drinking water, surface water, and groundwater in the 1990s, entitled "Historical Occurrence of Acephate, Azinphos-methyl, Chlorpyrifos, Diazinon, and Malathion in Waters of the United States, 1990-1997", (Cheminova, 1999, MRID 44887901).

- A monitoring study of finished drinking water that is currently in progress being conducted by the OP Case Study Group, of which Cheminova is a member. This study includes both malathion and malaoxon measurements.

These data represent substantially higher quality measurements than EPA's Pesticides in Groundwater Database, and they are more accurate representations of reality than GENEEC modeling results.

1. Historical Monitoring Data

As mentioned above, Cheminova has recently conducted an extensive survey of available water monitoring data. This report, entitled "Historical Occurrence of Acephate, Azinphos-methyl, Chlorpyrifos, Diazinon, and Malathion in Waters of the United States, 1990-1997," was submitted to EPA on July 29, 1999 (Cheminova, 1999, MRID 44887901). This report provides an extensive summary of malathion concentrations in finished drinking water, surface water bodies, and groundwater in high use areas of the United States from 1990 to 1997. The review was limited to data beginning in 1990 because there have been significant improvements in the analysis of pesticides in water over time, and including only data collected in the 1990s ensures that the limit of quantification (LOQ) is generally in the sub-part per billion (ppb) range.

The report summarized data from several sources, including:

- Data generated under The Safe Drinking Water Act (SDWA), which requires states to monitor for a variety of contaminants in finished drinking water, including both at the treatment plant and from groundwater sources used for drinking water. While states are not required to monitor for malathion, a number of states in areas of high pesticide usage have included malathion in their SDWA analyses.

- The United States Geological Survey (USGS) National Water Quality Assessment Program (NAQWA) which includes measurements of concentrations in river basins and aquifers across the nation.

- EPA's Storage and Retrieval (STORET) system, which is an EPA database of a large variety of surface and groundwater data collected by federal, state, and local agencies.

- Additional data from state agencies that may not be included in the other databases.

- Data reported in the public literature, including data collected by academic researchers.

For malathion, there were 6,543 finished drinking water samples reported, including both groundwater and surface water samples. Only 10 of these samples (0.15%) had detectable concentrations, and the highest concentration was 0.20 ppb. If a zero concentration is substituted for the samples below the LOQ, the average malathion concentration was 0.0019 ppb. Cheminova believes that these results provide the most reliable data for assessing drinking water concentrations for risk assessment.

In non-drinking water, there were 23,765 malathion samples in both groundwater and surface water. Only 729 of these samples (3.1%) had detectable concentrations of malathion. Malathion was detected in only 1.42% of groundwater and 3.81% of surface water samples. If the mean is calculated by substituting zeros for non-detectable results, the mean concentrations are 0.0023 ppb and 0.0032 ppb in groundwater and surface water, respectively. If the non-detectable results are assigned values equal to one-half the LOQ, the mean concentrations were 0.11 ppb in groundwater and 0.042 ppb in surface waters.

The report also contains data on the simultaneous occurrence of two or more of the five organophosphate insecticides (OPs) in the same sample. There was no co-occurrence of any of the five OPs (acephate, azinphos-methyl, chlorpyrifos, diazinon, and malathion) in any drinking water samples. In non-drinking water, two or more OPs occurred at the same time in 1.2% of groundwater samples and 9.6% of surface water samples. These data are useful for considering the possibility of cumulative drinking water risk from OPs.

Cheminova believes that this report presents a synthesis of reliable historical water monitoring data demonstrating that there is virtually no exposure to malathion in finished drinking water derived from groundwater and surface water sources. Therefore, Cheminova believes this report demonstrates that exposure to malathion in drinking water should not be a concern for the Agency.

2. OP Case Study Group Drinking Water Monitoring Data

The OP Case Study Group is a consortium of companies that produce organophosphate pesticides, including Novartis Crop Protection, Bayer, Dow Agrosciences, Cheminova, and Valent U.S.A., that is addressing a variety of science issues related to FQPA. This group has sponsored a nationwide measurement study of organophosphates and their major degradation products in community water supplies (i.e., finished drinking water at the treatment plant). The study includes periodic measurements over a 1-year time frame at 30 community water supplies in areas with substantial agricultural pesticide use, and 20 community water supplies in urban areas where there is substantial non-agricultural pesticide use.

Although the results of the study are still preliminary, some sampling has occurred at all of the sites. Thus far, there have been no detections of malathion or malaoxon. These recently collected data are consistent with the historical review of detections of malathion in drinking water that show that malathion is only very rarely detected in drinking water.

C. CRITIQUE OF DETECTIONS IN PESTICIDES IN GROUNDWATER DATABASE

To estimate a groundwater drinking water concentration, EPA has relied on measurements reported in EPA's Pesticides in Groundwater Database, which summarizes measurements from federal, state, and local agencies from 1971 to 1991. Cheminova has submitted a document that demonstrates that most of the malathion detections in this database are highly questionable. This document, entitled "Overview of the Environmental Behavior of Malathion and Response to EPA's Reviews of Malathion Environmental Fate Studies," was submitted in December of 1993 (Severn, 1993, MRID 43166301). A brief overview of the information provided in this document regarding the Pesticides in Groundwater Database measurements of malathion is provided below.

The Pesticides in Groundwater Database reports results for 3,252 wells monitored nationwide. Of these wells, only 12 had detectable levels of malathion, and 8 of these 12 wells were in Westmoreland County, Virginia. Cheminova believes that the Westmoreland County measurements are questionable for the following reasons:

- **Use Patterns.** The Westmoreland County study report includes a complete list of the pesticides that were applied to the farms in the watershed; no malathion use was reported.

- **Analytical Methods:** The multiresidue method used in this study used gas chromatography with a packed column and an electron capture detector. Other commonly used pesticides may have eluted very close to the retention time of malathion. Thus, the results of this analysis do not necessarily indicate the presence of malathion.

- **Known Environmental Behavior of Malathion:** The wells at this site are 25 to 45 feet from the surface. Malathion would need to persist for a significant period of time to allow it to be leached to these depths. The environmental fate data submitted by Cheminova demonstrate that malathion degrades very rapidly in both soil and water. In addition, the terrestrial field dissipation studies demonstrate that malathion does not move below 12 inches in soils.

Despite the use of more than 3 million pounds of malathion in California in recent years, there was only a single detection of malathion in groundwater in a single detection in well water. A follow-up sample from this single well reported no detections.

There have been substantial improvements in analytical measurement technology over the past decades. Cheminova believes that the groundwater data assembled by Cheminova are

more accurate than the data in the Pesticides in Groundwater Database because they were collected more recently and analyzed with highly sophisticated measurement methods.

The data presented in this section demonstrate that malathion and malaoxon are rarely detected in drinking water, and that drinking water exposure to these chemicals is not a concern. As EPA moves toward preparing the cumulative risk assessments mandated by FQPA, it will become more important to provide realistic estimates of drinking water exposure. The data presented in this document provide the best source of information to meet FQPA's "reliable information" criteria.

VIII. OCCUPATIONAL AND RESIDENTIAL EXPOSURE RISK ASSESSMENTS

Cheminova has the following comments related to EPA's occupational and residential risk assessments included in EPA's preliminary draft RED for malathion.

A. EPA INCLUDED TWO RISK ASSESSMENTS IN ITS PRELIMINARY DRAFT RED.

In its draft RED, EPA included two versions of the occupational and residential risk assessment. These documents are the September 16, 1999 (9/99), "Malathion: Occupational and Residential Exposure and Risk Assessment for the Reregistration Eligibility Decision (RED) Document" and the February 10, 2000 (2/00), "Malathion: Preliminary Risk Assessment for the Reregistration Eligibility Decision (RED) Document, Revised to Include Cancer Assessment Review Committee Conclusions." Substantively, these documents are the same, although they are organized differently and some differences were noted. Selected differences between the documents are highlighted below.

The existence of two risk assessments results in considerable confusion in trying to understand the differences and similarities between them, as well as confusion about which version represents EPA's position on the potential occupational and residential risks of using malathion. Therefore, Cheminova requests that any revisions to the risk assessment be presented in just one document.

In this section of Cheminova's comments, except where otherwise noted, page numbers refer to the September 16, 1999, risk assessment document because it is generally written in greater detail.

1. Differences Between the 9/99 and 2/00 Malathion Risk Assessments

a. Helicopter Application Exposures

Consistent with current HED policy, EPA did not include exposure estimates for aerial application by helicopter in the 2/00 risk assessment, whereas such estimates were included in the 9/99 risk assessment. As HED's risk assessment chapter notes, HED policy excludes this scenario because the Pesticide Handlers Exposure Database (PHED) data upon which it

is based are insufficient for meaningful results. Therefore, PHED data for helicopters should not be used to calculate exposures for this scenario. As a surrogate, Cheminova recommends that mixer/loader and applicator exposures associated with aerial application by helicopter be assumed to be qualitatively similar to those for fixed-wing aircraft.

b. Exposure Estimates

The estimated exposures, aggregate risk indices, and cancer risks for some scenarios are different in the 9/99 and 2/00 risk assessment documents. Sufficient detail (e.g., unit exposures and application rates) is provided in the 9/99 report to confirm the calculations, but sufficient information is not readily available in the 2/00 report. Due to the lack of detail in the 2/00 risk assessment, it is not possible to understand why some of the exposures and risks reported there do not match those reported in the 9/99 risk assessment. Cheminova requests that EPA double-check all calculations for the scenarios listed below. In addition, the risk assessment report should provide sufficient information so that readers can understand how all exposure calculations were performed. Cheminova requests that EPA present at least the level of detail provided in the 9/99 risk assessment in the revised risk assessment.

Cheminova has identified several examples in which the exposure and risk calculations do not match in the two reports including the following:

- The exposures and the Aggregate Risk Indices (ARIs) associated with ULV spray applications for mosquito control in the two reports do not match. From Table 18 in the 2/00 risk assessment (which presents cancer risks), it appears that the mosquito control scenarios were calculated assuming an application rate of 0.23 lb a.i./acre, whereas an application rate of 0.50 lb a.i./acre was assumed in the 9/99 assessment. Cheminova requests that EPA use the application rate of 0.23 lb a.i./acre in the revised risk assessment.

- For applying sprays with a groundboom sprayer, the cancer risk estimates for several crops do not match in the 9/99 and 2/00 risk assessments. The crop groups for which there is a discrepancy are: "ag (pumpkins)," "ag (veg)," "ornamentals," and "golf course turf." Cheminova requests that EPA double-check these calculations.

B. OCCUPATIONAL APPLICATION EXPOSURE AND RISK ASSESSMENT

In this section of Cheminova's comments, except where otherwise noted, page numbers refer to the September 16, 1999, risk assessment document because it is generally written in greater detail.

1. Supported Crops and Uses

EPA assessed occupational and residential exposures for application of malathion to lawns, including golf courses, sod farms, and ornamental lawns. However, as Cheminova pointed out in a March 10, 1998, letter to EPA, Cheminova is not supporting applications of malathion to residential lawns, ornamental lawns, or golf courses. Therefore, Cheminova requests that EPA remove these scenarios from its risk assessment.

2. Agricultural Crop Groups and Assumed Application Rates

Malathion is registered for use on a very large number of crops. Cheminova recognizes the necessity of creating groups of similar crops in order to simplify the occupational exposure assessment. However, the crop groups utilized by EPA in the draft occupational and residential risk assessment are difficult to understand and frequently incorrect.

The names given to EPA's crop groups are particularly confusing. For the typical reader, the crop group names "ag fruit and nuts," "ag pumpkin," "ag citrus fruits," and "ag veg" do not have much meaning. Furthermore, some tables in the occupational risk assessment refer to "ag med" and "ag low" as crop groups, but these are not defined in the text.

In some cases, the crop groups are not logically constructed. For example, EPA's "ag citrus" group is listed as being composed of apricots, cherries, peaches, and nectarines on page 8. These crops are stone fruits; thus they should not be combined with the citrus fruits. It is not clear if EPA has actually included any citrus fruits in the "ag citrus group."

Finally, the maximum application rates assumed for each of these crop groups do not correspond to the maximum application rates that were tested in residue studies. For example, EPA assumed a maximum application rate of 6 lb a.i./acre for EC formulations on the "ag fruit and nut" group, but the maximum tested rate for pineapples, apples, and pecans is 5.0 lb a.i./acre. Similarly, EPA assumed a maximum application rate of 2 lb a.i./acre for EC formulations on the "ag pumpkin" group, but the maximum tested rate for pumpkins, melons, and eggplant is 1.0 lb a.i./acre. In some cases, EPA assumed an application rate that is actually less than what it should have been. For example, EPA assumed an application rate of 0.5 lb a.i./acre for EC formulations on the "ag veg" group, but many crops in that group have maximum application rates of 1.25 and 2.5 lb a.i./acre.

Cheminova recommends that EPA include in its risk assessments tables similar to the tables presented in Section V of this document. In order to simplify the exposure calculations for the operator exposure, Cheminova recommends that the agricultural crops be organized according to the crop groupings specified in 40 CFR, Part 180.

In Table 11 below, Cheminova has identified the maximum tested application rate for each agricultural crop group and formulation. Cheminova requests that EPA perform its occupational exposure assessment using the crop groupings identified in 40 CFR, Part 180 and the maximum tested application rates identified below in Table 11. In the interest of

simplifying the risk assessment, where possible, broader crop groups could be created when the methods of application, the maximum application rates, and the number of applications per season are the same. For example, root and tuber vegetables could be combined with bulb vegetables. For EC formulations, a group could be composed of cereal grains, the grass forage group, and nongrass animal feeds. In addition, EPA should reconfigure its exposure assessment to include only appropriate application methods for each crop group (e.g., airblast application is not appropriate for root and tuber vegetables, etc.).

Table 11. Maximum Proposed Application Rates of Malathion, Organized by Agricultural Crop Group and Formulation

Crop Group	Maximum Tested Application Rate (given in lb a.i./A unless otherwise noted) by Formulation				
	EC	ULV	RTU	WP	Dusts
Root and Tuber Vegetables	1.56	- -	- -	- -	- -
Bulb Vegetables	1.56	- -	- -	- -	- -
Leafy Vegetables (except Brassica)	2.0	- -	- -	- -	- -
Brassica Vegetables	1.25	- -	- -	- -	- -
Legume Vegetables	2.5	0.61	- -	- -	- -
Fruiting Vegetables (except Cucurbits)	3.5	- -	- -	- -	- -
Cucurbit Vegetables	1.88	- -	- -	- -	- -
Citrus Fruits	6.25 [A]	0.92	- -	- -	- -
Pome Fruits	1.25	- -	- -	- -	- -
Stone Fruits	3.75	1.22	- -	- -	- -
Berries	2.0	0.76	- -	2.0	2.0
Tree Nuts	5.0	- -	- -	- -	- -
Cereal Grains	1.25	0.61	- -	- -	- -
Grass Forage, Fodder, and Hay Group	1.25	0.92	- -	- -	- -
Nongrass Animal Feeds	1.25	0.61	- -	- -	- -
Miscellaneous Commodities	5.0 (pineapples) 2.50 (cotton)	1.22 (cotton)	1.15 (cotton)	- -	- -
Mushrooms	0.039 lb a.i./1,000 ft^2.	- -	- -	- -	- -
Stored grains	- -	- -	- -	- -	0.62 lb a.i. per 1,000 bushels or 0.31 lb a.i./1,000 ft^2.

3. Application Rates on Ornamentals, Shade Trees and Pine Trees

EPA assumed an application rate of 2.6 lb a.i./acre for ornamentals and pine trees. Cheminova is unsure how this application rate was derived and asks that EPA explain its derivation from the values required by the labels (see below).

EC formulations are labeled for application to flowers, ornamentals, shade trees, and forestry uses. Cheminova notes the following:

- For EC formulations, the application rate on ornamentals, flowers, and shade trees is specified as the quantity of product to be mixed in 100 gallons of water. The amount of spray to apply per acre is not specified on the labels. The maximum application rate for the 8EC formulation is 1.25 pints per 100 gallons (1.25 lb a.i./100 gal), and the maximum application rate for the 5EC formulation is 4 pints per 100 gallons (2.5 lb a.i./100 gal). Assuming a spray rate of 100 gallons per acre, these application rates would correspond to 1.25 and 2.5 lb a.i./acre.

- For forest uses, the maximum application rate for the EC formulation is 0.9375 lb a.i./acre. For ULV formulations, the maximum label application rate for forest uses is 1.0 lb a.i./acre.

The maximum application rates for malathion on ornamentals and for forestry uses are clearly different. Cheminova suggests that EPA separate the ornamental and forestry uses in the risk assessment in order to more accurately assess exposures and risks associated with each major use.

4. Application Rate for Mosquito Control

EPA assumed a maximum application rate of 0.5 lb a.i./acre for EC sprays for mosquito control. A review of labels suggests that this rate is applicable for thermal foggers. The maximum labeled application rate for EC sprays is 0.6 lb a.i./acre.

In the 9/99 risk assessment, EPA states that the maximum application rate for ULV applications is 0.5 lb a.i./acre. Cheminova is unsure of the source of this application rate. As EPA has noted, the maximum application rate for ground foggers is 0.11 lb a.i./acre, and the rate for aerial ULV application is 0.23 lb a.i./acre. Since EPA based the postapplication assessment on these latter application rates, it is unclear why the mixer/loader/applicator assessment was based on an application rate of 0.5 lb a.i./acre. Cheminova notes that the 2/00 risk assessment utilized an application rate of 0.23 lb a.i./acre for ULV sprays for mosquito control. Cheminova suggests that EPA revise the exposure assessment to reflect the appropriate maximum application rate for ULV applications for mosquito control.

5. Application Rate for Berries

EPA assumed a maximum application rate of 4 lb a.i./acre. However, as is shown in Table 11, the maximum tested application rate for berries is 2 lb a.i./acre for EC and WP formulations and 0.76 lb a.i./acre for ULV formulations. Cheminova recommends that EPA revise its risk assessment to reflect these application rates.

6. Baseline Exposure Scenario

In the occupational risk assessment, EPA has evaluated risks for three mitigation scenarios:

(1) Baseline – representing exposure to an operator wearing long-sleeved shirt and long pants;

(2) PPE-Mitigated – representing exposure to an operator wearing personal protective equipment (PPE); and

(3) Engineering Controls – representing exposure to an operator associated with use of engineering controls (closed systems, enclosed cabs, water-soluble bags for wettable powder formulations, etc.).

The baseline exposure scenario used by EPA violates the label PPE requirements and represents an illegal use of malathion. Cheminova urges EPA to remove baseline scenario exposure calculations from the risk assessments because their inclusion may mislead the public about the potential risks of using malathion.

7. Occupational Exposure Scenarios

EPA included occupational exposure scenarios that should not be included in the risk assessment. Each of these scenarios is discussed individually below.

EPA inappropriately included a scenario – (7) applying sprays with a helicopter – in the 9/99 risk assessment. As HED's risk assessment chapter notes, HED policy excludes this scenario because the PHED data upon which it is based are insufficient for meaningful results. PHED contains only three replicates for this scenario, whereas a minimum of 15 replicates of suitable quality are required to generate a meaningful exposure estimate. Therefore, exposures should not be calculated for this scenario, and Cheminova requests that EPA not include such calculations in the risk assessment. Cheminova notes that the 2/00 risk assessment is consistent with current HED policy on this point and does not present exposures or risks associated with aerial application by helicopter. As a surrogate, Cheminova recommends that mixer/loader and applicator exposures associated with aerial application by helicopter be assumed to be qualitatively similar to those for fixed-wing aircraft.

EPA included an exposure scenario – (11) applying with a handgun to turf – that does not represent an application method that is being supported for reregistration by Cheminova. Cheminova requests that EPA eliminate this exposure scenario from its risk assessment.

EPA has included an exposure scenario – (15) mixing/loading/applying with a paintbrush for mosquito control – that does not appear to be appropriate in the occupational risk assessment. Cheminova is unaware of any formulation labels that allow application by paintbrush to achieve mosquito control. Cheminova is, however, aware of EC formulation labels that refer to spraying painted and unpainted surfaces around dwellings and buildings to achieve mosquito control. Cheminova requests that EPA clarify what labels support this exposure scenario. Unless the appropriateness of this scenario can be demonstrated, Cheminova requests that this scenario be omitted from the risk assessment.

The flagger scenario (16) is too broadly defined. Flaggers are assumed to be present for aerial applications on agricultural crops with both EC and ULV formulations and for mosquito control with both EC and ULV formulations. Given the very high treatment areas for mosquito control (1,500 acres for EC formulations and 7,500 acres for ULV formulations), use of human flaggers for mosquito control applications is not feasible. In fact, discussions with Lee County Mosquito Control in Florida indicate that flaggers have not been used during applications for mosquito control for more than 20 years. It is much more likely that GPS or other technical guidance systems would be used in mosquito control applications. Therefore, EPA should eliminate the evaluation of human flaggers for mosquito control.

8. Assumptions for Daily Acres and Volumes Treated

a. Low-Pressure Handwand

EPA assumed that a low-pressure handwand would be used to treat 5 acres of ornamentals. In recent risk assessments for other pesticides (e.g., dimethoate), EPA assumed a volume-based application rate of 40 gallons per day. Unless there is a rationale for the different value assumed in the malathion risk assessment, Cheminova requests that EPA recalculate all low-pressure handwand scenarios assuming a use rate of 40 gallons per day.

b. Backpack Sprayer

EPA assumed that a backpack sprayer would be used to treat 5 acres of ornamentals. In recent risk assessments for other pesticides (e.g., dimethoate), EPA assumed a volume-based application rate of 40 gallons per day. Unless there is a rationale for the different value assumed in the malathion risk assessment, Cheminova requests that EPA recalculate all backpack sprayer scenarios assuming a use rate of 40 gallons per day.

c. Handgun Sprayer

EPA has assumed a treatment rate of 5 acres per day when applying malathion to turf using a handgun sprayer. This scenario should be removed from the assessment because Cheminova is not supporting turf applications for reregistration.

9. PPE Assumptions

Cheminova recognizes that the personal protective equipment (PPE) requirements on current malathion product labels are inconsistent. At present, most Cheminova labels require that handlers wear long-sleeved shirts, long pants, socks, shoes, and chemical- or water-resistant gloves. Additional requirements seen on some current labels include headgear for overhead exposures and protective eyewear. Cheminova will be holding discussions with stakeholders to determine a consistent set of PPE requirements for malathion products. In addition to the current minimum requirements, options being considered include coveralls and dust/mist filtering respirators. Cheminova will advise EPA of the outcome of these discussions at the nearest opportunity in the hope that EPA will incorporate the PPE requirements in the revised risk assessment.

Cheminova notes that EPA applied PPE assumptions in an effort to generate acceptable exposures for the various scenarios. For example, gloves were assumed for some scenarios and respirators were included in others. EPA's resultant exposure assessment utilized a variety of assumptions regarding PPE. However, Cheminova requests that EPA include a single set of PPE requirements consistently throughout its risk assessment. There will be no need for EPA to estimate exposures based on incremental PPE requirements because the minimum set will have been determined by Cheminova.

10. Unit Exposure Calculations

a. Enclosed Cab Airblast Application

For enclosed cab scenarios, EPA assumed that applicators would not wear PPE, which is consistent with the Worker Protection Standard (WPS). However, there are no data in PHED to estimate enclosed cab, "no gloves" hand exposure for airblast application. Therefore, EPA estimated the enclosed cab, "no gloves" hand exposures by back-calculating from the enclosed cab, "gloves" hand exposure assuming a 90% reduction factor for wearing gloves. Thus, EPA estimated a total dermal unit exposure of 0.14 mg/lb a.i. for enclosed cab airblast application.

However, on page 10 of the PHED Surrogate Exposure Guide, a protection factor of 98% is recommended to estimate exposure reduction associated with enclosed cabs. Therefore, Cheminova proposes estimating the enclosed cab, "no gloves" hand exposure for airblast sprayer application by applying a 98% reduction factor to the open cab, "no gloves" hand exposure. If this approach is taken, the estimated total dermal unit exposure is 0.0085 mg/lb

a.i. Cheminova recommends that EPA use this value to estimate dermal exposures associated with enclosed cab airblast application.

For comparison, Cheminova examined another approach to estimating the enclosed cab "no glove" dermal unit exposure. Application of the 98% reduction factor to the total dermal unit exposure from the open cab, "no gloves" scenario would result in an estimated dermal unit exposure of 0.0078 mg/lb a.i. for the enclosed cab scenario. Thus, Cheminova has calculated similar unit exposure estimates for enclosed cab airblast application from data in the PHED Surrogate Exposure Guide using two different methods. Therefore, Cheminova believes that its estimate of 0.0085 mg/lb a.i. is reasonable and that EPA's estimate, 0.14 mg/lb a.i., is inappropriate.

b. Fogger Application

Because PHED contains no data appropriate for estimating exposures associated with application by foggers, EPA used the unit exposure estimates for airblast application as a surrogate. Cheminova believes this is a reasonable assumption given the lack of data. However, Cheminova suggests that, for enclosed cab application, EPA use the dermal unit exposure estimate of 0.0085 mg/lb a.i. as calculated above rather than EPA's estimate of 0.14 mg/lb a.i.

c. Paintbrush Application

As previously discussed above, Cheminova is unaware of any formulation labels that allow paintbrush application for mosquito control. Consequently, Cheminova requests that this scenario be removed from the risk assessment.

d. Hose-End Sprayer

In Table 3, EPA states that there are no data with which to estimate a unit exposure for hose-end sprayer application for the PPE-mitigated scenario. Cheminova notes that EPA did not present PPE-mitigated exposures for this scenario because the baseline scenario risks were acceptable. However, because Cheminova believes that baseline scenario calculations are potentially misleading and should therefore be removed from the risk assessment, Cheminova requests that EPA estimate PPE-mitigated exposures for this assessment using the dermal unit exposure calculated below.

Cheminova notes that there are limitations to the dataset underlying the PHED Surrogate Exposure Guide exposure estimates for hose-end sprayer application. There are only eight replicates, and the resulting exposure estimate is of very low quality. For the "single layer, gloves" scenario, PHED does not contain any body or hand data. However, the PHED Surrogate Exposure Guide suggests that the action to take in such circumstances is to estimate the dermal exposure by applying a reduction factor of 50% to the dermal exposure estimate to account for a single layer of clothes and to apply a reduction factor of 90% to the "no gloves" hand exposure to account for the gloves. If these reduction factors are applied,

the total dermal exposure is estimated to be 6.0 mg/lb a.i. Cheminova suggests that EPA include this estimated dermal exposure value in its exposure assessment of hose-end sprayer application scenarios.

e. Flagging for Aerial Application

Under the engineering controls scenario for flagging exposures, the inhalation unit exposure is incorrect in the 9/99 risk assessment. EPA lists an inhalation unit exposure of 0.35 µg/lb a.i. for enclosed cab flagging. However, because EPA used the enclosed cab unit exposures for groundboom application as a surrogate for flagging (due to the lack of appropriate PHED data), the inhalation unit risk should have been 0.043 µg/lb a.i. In the 2/00 risk assessment, it appears that this error may have been corrected.

11. Cancer Risk Assessment

In Tables 8, 9, and 10, EPA has calculated the LADD using the assumption of either 80 or 40 days of exposure per year to describe a handler's exposure frequency to malathion products. Footnotes to these tables state that the assumed "[n]umber of exposure per year is based on the maximum number of applications supported by residue field trial data." A review of the field residue testing, however, indicates that the maximum number of applications allowed per year on various crops ranges from as low as 2 for potatoes to as much as 25 for cotton. In most cases, the maximum applications per year number no more than 7. In no case are values of 40 and 80 days supported by the residue field testing data. Cheminova requests that EPA use crop-group specific data on the maximum number of applications allowed per year to estimate LADDs.

In Tables 8, 9, and 10, oftentimes the total daily dose and LADD are presented to only one significant figure (e.g., 0.05 and 0.01), and the total cancer risk is presented to three significant figures (e.g., 7.74e-06). For consistency, Cheminova suggests that EPA revise the calculations to present all values to two significant figures. In any case, it is not appropriate to present cancer risk estimates to a degree of precision that is not associated with the inputs that went into generating the estimates. Unit exposures are specified to two significant figures, so the associated cancer risks should not contain more than two significant figures. Cheminova notes that these errors in presentation of significant figures also appear throughout the 2/00 risk assessment.

12. Cancer Risk Assessment Summary

In the summary of the cancer risks (page 58), EPA states that cancer risks less than 10^{-6} do not trigger HED concerns and that attempts are made to mitigate cancer risks to at least 10^{-4}. It is not clear what standard EPA is applying here. Baseline scenario risks are compared to 10^{-4}, but risks for the PPE-mitigated and engineering control scenarios are compared to 10^{-6}. Cheminova is unsure why mitigated risks must be less than 10^{-6} when the stated goal is to mitigate risks to less than 10^{-4}. Cheminova requests that EPA clarify the policy regarding cancer risks and revise the cancer risk assessment accordingly.

C. Occupational Postapplication Exposure and Risk Assessment

1. Postapplication Exposure Scenarios

As stated previously, Cheminova is not supporting applications of malathion to turf. Therefore, Cheminova requests that all postapplication scenarios concerning potential dermal exposures to treated turf be removed from the occupational postapplication risk assessment.

2. Crop Groups and Application Rates

EPA applied the default transfer coefficients to crop groups in the occupational postapplication risk assessment. Cheminova suggests that the reentry risk assessment be revised to reflect the maximum application rates and crop groups recommended for the occupational risk assessment.

A further refinement of the postapplication assessment would allow for the most complete understanding of potential postapplication risks on a crop-by-crop basis. To accomplish this, Cheminova requests that EPA assess postapplication exposures for the application of each formulation onto each crop at the crop-specific application rate and using the most relevant transfer coefficients. Cheminova believes that the crop group approach employed by EPA does not provide sufficient detail to completely understand postapplication risks and the appropriate reentry intervals.

EPA assumed an application rate of 2.0 lb a.i./acre on mushrooms in the postapplication assessment; however, the application rate for mushrooms, 0.039 lb a.i./1,000 ft^2, is equivalent to 1.7 lb a.i./acre. Cheminova requests that EPA recalculate postapplication exposures for mushrooms using the correct application rate.

3. Transfer Coefficients

EPA applied the default transfer coefficients to crop groups in the occupational postapplication risk assessment. Where available, EPA should use the transfer coefficients measured in a number of studies conducted by the Agriculture Reentry Task Force (ARTF), of which Cheminova is a member. Cheminova believes that the ARTF transfer coefficients demonstrate that the EPA defaults considerably overstate the true values.

EPA's transfer coefficients are contained in its May 7, 1998, Science Advisory Council for Exposure Policy #3, Agricultural Default Transfer Coefficients. This memorandum provides a list of default transfer coefficients for use in postapplication assessments, which the memorandum acknowledges are not supported by data:

> The generic default values in the table below are not supported quantitatively, but were derived by pesticide exposure assessors, based on their best judgement from their experience with the transfer coefficients used for these crops and agricultural activities in pesticide-specific assessments.

The ARTF data provide substantially more accurate transfer coefficients for exposure assessment than EPA's "best judgement" values. Therefore, Cheminova recommends that EPA use the ARTF values. If EPA has not yet reviewed these ARTF data, it should wait until such reviews are completed before making any decisions about malathion reentry intervals.

To illustrate the differences between the EPA default transfer coefficients and those measured by ARTF, consider the following examples:

- For grape harvesting, EPA used a transfer coefficient of 15,000 cm^2/hr, while the ARTF data support a transfer coefficient of 1,500 cm^2/hr.

- For apples, EPA used a transfer coefficient of 10,000 cm^2/hr for all activities. The ARTF data support transfer coefficients of 2,771 cm^2/hr for apple thinning, 1,491 cm^2/hr for harvesting, and 96 cm^2/hr for apple propping. The apple thinning (ARTF 1996, MRID 42428101) and grape harvesting (ARTF 1997b, MRID 43223904) studies have been submitted to the Agency for review. ARTF plans to submit the apple harvesting study (ARTF No. 025) and the apple propping study soon.

4. Postapplication Occupational Cancer Risks

In the postapplication occupational assessment, LADDs were estimated assuming that exposures would occur 40 days per year. Cheminova is unsure how EPA derived the value of 40 days to describe postapplication exposure frequency. Cheminova's review of the field residue testing indicates that the maximum number of applications allowed per year on various crops ranges from as low as 2 for potatoes to as much as 25 for cotton. In most cases, the maximum applications per year number no more than 7. In no case, are values of 40 and 80 days supported by the residue field testing data. Cheminova requests that EPA use crop-group specific data on the maximum number of applications allowed per year to estimate LADDs.

5. Presentation of Postapplication Results

In the 9/99 risk assessment, exposures and MOEs are explicitly calculated for each day following application. In the 2/00 risk assessment, however, this detail is lost, and the only information presented consists of a summary of estimated reentry intervals. Cheminova finds the approach in the 2/00 assessment to be lacking in detail, and it obscures the calculations made for the postapplication assessment. Therefore, Cheminova requests that EPA include occupational postapplication calculations in the revised risk assessment.

D. RESIDENTIAL APPLICATION EXPOSURE AND RISK ASSESSMENT

1. Exposure Assumptions

In the residential exposure assessment, EPA made several inappropriate assumptions regarding the rates of use for homeowners.

a. Lawn Application

As stated above, Cheminova is not supporting application of malathion products to turf, either by homeowners or commercial applicators. Therefore, all residential scenarios involving the application of malathion to turf should be removed from the residential exposure and risk assessment.

b. Hose-End Sprayer Application

EPA assumed that homeowners would apply 50 gallons of spray with a hose-end sprayer for use on fruit trees, ornamentals, vegetables/small fruit gardens, and mosquito control. However, no rationale was provided for the departure from the default assumption from EPA's 1997 Standard Operating Procedures (SOPs) for Residential Risk Assessments of 5 gallons of spray per day for these uses. Cheminova requests that EPA revise the risk assessments to include the SOP default rate of 5 gallons of spray for hand-held spray equipment.

c. Body Weight

In the residential exposure assessment, EPA assumed an average body weight of 70 kg. However, the SOPs recommend an average body weight of 71.8 kg. Cheminova requests that EPA incorporate the appropriate default value for body weight into the residential exposure assessment.

d. Application Rates for Homeowner Uses

EPA has assumed incorrect application rates for homeowner uses of EC formulations on fruit trees, ornamentals, and vegetables.

- For fruit trees, EPA lists a maximum application rate of 0.034 lb a.i./gallon, but the maximum rate obtained from a Cheminova product label is 0.030 lb a.i./gallon (2 tablespoons Malathion 50 Plus per gallon).

- For ornamentals, EPA lists a maximum application rate of 0.034 lb a.i./gallon, but the maximum rate obtained from a Cheminova product label is 0.030 lb a.i./gallon (2 tablespoons Malathion 50 Plus per gallon).

- For vegetables, EPA lists a maximum application rate of 0.023 lb a.i./gallon; however, the maximum rate obtained from a Cheminova product label is 0.020 lb a.i./gallon (4 teaspoons Malathion 50 Plus per gallon).

E. RESIDENTIAL POSTAPPLICATION EXPOSURE AND RISK ASSESSMENT

1. Turf-Related Exposure Scenarios

EPA calculated postapplication exposures to residents contacting treated turf. However, because Cheminova is not supporting reregistration of malathion for treatments to turf, these postapplication exposures should be removed from the exposure assessment.

Cheminova recognizes that spraying malathion to achieve mosquito control may result in residues being present on turf. Consequently, Cheminova believes that postapplication exposure scenarios involving turf should be limited to those involving residues resulting from mosquito control spraying.

2. Deposition Following Mosquito Control Uses

EPA used AgDRIFT to estimate the deposition of malathion following aerial spraying. Unfortunately, EPA did not provide any information in the residential postapplication exposure assessment about the inputs that were used in the AgDRIFT model. According to an explanatory note on page 84, it appears that the deposition rate of malathion following aerial application was calculated by EPA to be 35%. Cheminova believes that the risk assessment report should explain how this estimate was derived and what inputs and model parameters were used in generating it. Otherwise, the public cannot understand how the estimate was made.

3. Body Weight Assumption

In the residential postapplication exposure assessment, EPA assumed an average body weight of 70 kg. However, the SOPs recommend an average body weight of 71.8 kg. Cheminova requests that EPA incorporate the correct default value for body weight into the residential postapplication exposure assessment.

4. Application Rate Assumptions

In estimating the dislodgeable foliar residues (DFRs) for malathion on garden plants and pick-your-own strawberries, EPA assumed that 5 gallons of spray (0.023 lb ai/gal) would be applied to an area of 1,000 ft^2. At this rate, the application on strawberries is equivalent to 5.0 lb a.i./acre, which is considerably greater than the maximum rate of 2.0 lb a.i./acre. EPA also assumed that 5 gallons of spray (0.034 lb ai/gal) would be applied to ornamentals in an area of 2,000 ft^2. At this rate, the application on ornamentals is equivalent to 3.7 lb a.i./acre, which is considerably greater than the 2.6 lb a.i./acre value that EPA used in the occupational exposure assessment. Furthermore, the SOPs state that homeowner exposure assessments

assume 10,000 ft^2 for treatments based on area and 5 gallons of spray for treatments based on concentration. Thus, the SOPs support application of 5 gallons of spray to a total area of 10,000 ft^2. Cheminova suggests that DFRs for the residential postapplication exposure assessment be recalculated assuming either that 5 gallons of spray are applied to a total area of 10,000 ft^2 or that the maximum application rate is not exceeded. Again, as stated above, Cheminova believes that the application rates used by EPA are incorrect.

EPA has assumed an application rate of 0.023 lb a.i./gal for strawberries. However, the maximum labeled application rate is 0.030 a.i./gallon (2 tablespoons of Malathion 50 Plus per gallon). Cheminova requests that EPA revise the calculation of the DFR for strawberries based on this correct maximum application rate.

5. Cancer Risk Assessment Exposure Assumptions

EPA has assumed that all "residential" use of malathion would be associated with 5 postapplication exposure days per year. Cheminova is unsure of the foundation for this assumption. The assumption of 5 days per year at commercial "pick your own" strawberry farms appears to be too high.

IX. ENVIRONMENTAL FATE

With the exception of the issue discussed below, at this time, Cheminova has no comments on this section. Cheminova will provide the Agency with comments during the 60-day public comment period.

A. EFED'S USE OF DATA FROM THE OPEN LITERATURE

In its description of the environmental fate of malathion, EFED compares the results of registrant-submitted guideline studies to results from studies obtained from the open literature. EFED presents the information from the open literature in such a way that it appears to give equal weight to the results from the open literature studies. Cheminova believes that the registrant-submitted guideline studies, conducted in compliance with Good Laboratory Practices, and conducted with Cheminova's test material, should be given much more weight than studies from the open literature. If EFED wants to include information from the open literature, it should fully evaluate these open literature studies, provide data evaluation records for these studies, and include a discussion of the uncertainties associated with these studies like it does with the registrant-submitted studies.

X. RESIDUE CHEMISTRY

With the exception of the issue discussed below, at this time, Cheminova has no comments on this section. Cheminova will provide the Agency with comments during the 60-day public comment period.

A. TOLERANCES

EPA states that any crops for which no support for tolerances has been received by the Agency are considered revoked. While the use of malathion is not being supported on certain crops grown in the United States, any tolerances for these crops remain valid until they are revoked through rulemaking. Moreover, EPA should not initiate rulemaking proceedings to revoke any such tolerances until the issue of import tolerances has been resolved for these crops.

XI. ECOTOXICOLOGY

With the exception of the issue discussed below, at this time, Cheminova has no comments on this section at this time. Cheminova will provide the Agency with detailed comments during the 60-day public comment period.

A. EFED'S REFERENCES

Cheminova has been unable to obtain copies of several references listed in the EFED chapter. In many cases, the references cited by EFED are incomplete. EFED should provide complete references so that the cited articles can be obtained and independently evaluated.

Cheminova notes that many of the references cited by EFED are from university researchers, private researchers, and government agencies (some of which no longer exist). These studies are not guideline studies and they were not conducted in accordance with GLPs such that raw data are available for evaluation and verification of reported results. Furthermore, many of EFED's references were never published; therefore, Cheminova questions whether these citations were ever peer reviewed by the scientific community to determine the validity of the research.

Cheminova is concerned that it is not able to review these items in detail to determine the appropriateness of EFED's assumptions and conclusions based on information presented in these documents. Cheminova believes that it is critical that any references used by EFED are readily available to the public for review. Cheminova recommends that EFED consider making all of its references available in the public docket.

XII. CONCLUSIONS

Cheminova appreciates the opportunity to offer these comments and looks forward to working with EPA to resolve the many issues we have raised. We believe consideration of our comments will lead to the conclusion that any potential risks associated with the use of malathion are acceptable.

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